SEPTEMBER 2023

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

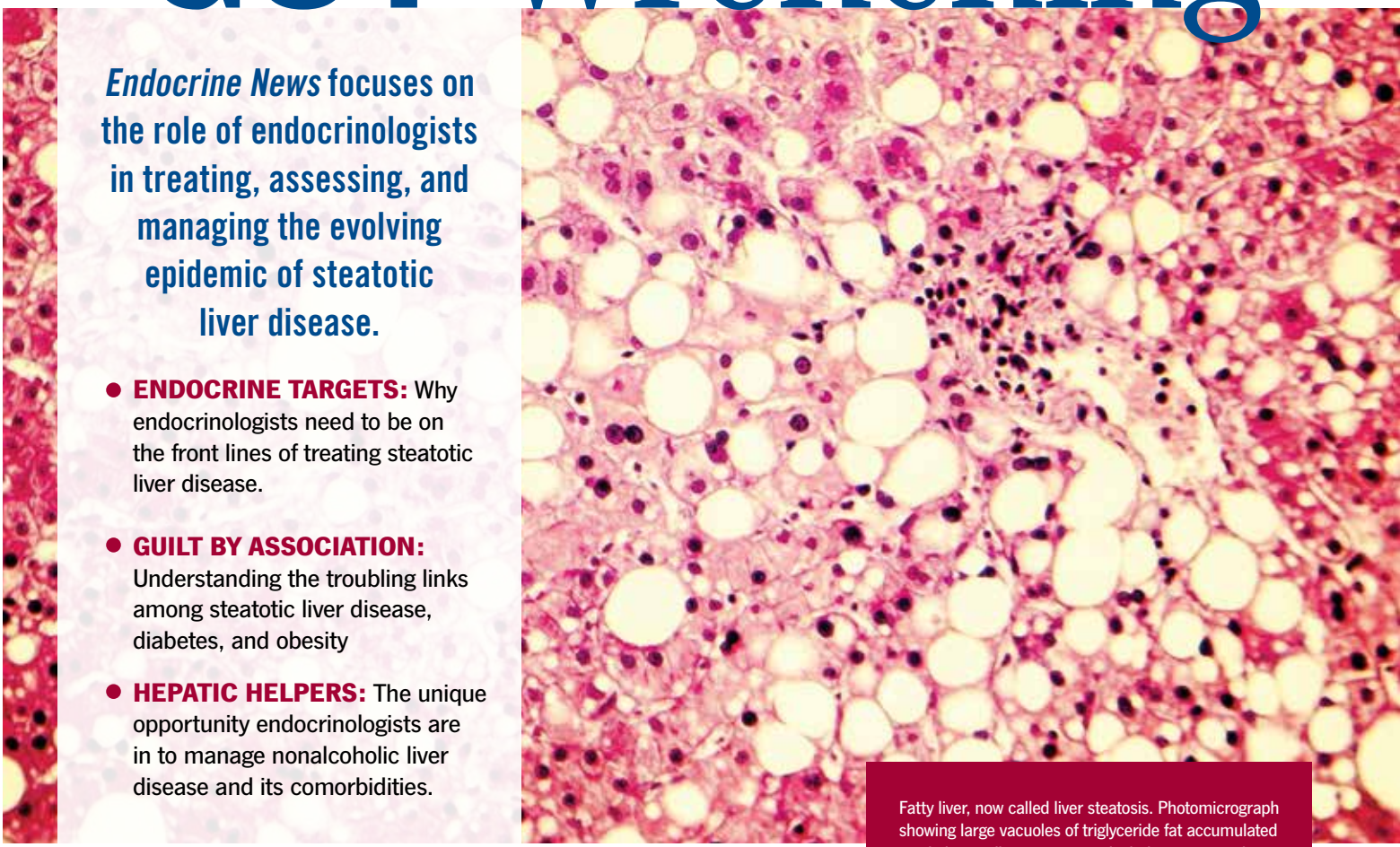
Endocrine news

INTERNATIONAL

GUT Wrenching

Endocrine News focuses on the role of endocrinologists in treating, assessing, and managing the evolving epidemic of steatotic liver disease.

- **ENDOCRINE TARGETS:** Why endocrinologists need to be on the front lines of treating steatotic liver disease.
- **GUILT BY ASSOCIATION:** Understanding the troubling links among steatotic liver disease, diabetes, and obesity
- **HEPATIC HELPERS:** The unique opportunity endocrinologists are in to manage nonalcoholic liver disease and its comorbidities.



Fatty liver, now called liver steatosis. Photomicrograph showing large vacuoles of triglyceride fat accumulated inside liver cells, it occurs in alcohol overuse, under action of toxins, in diabetes.

NAME CHANGE: NASH, MASH, MetALD, and more — how updated nomenclature avoids stigmatizing language and labels.

THE SILENT EPIDEMIC: Emerging research for detection and treatment of non-alcoholic fatty liver disease

ENDOCRINE SOCIETY

Hormone Science to Health

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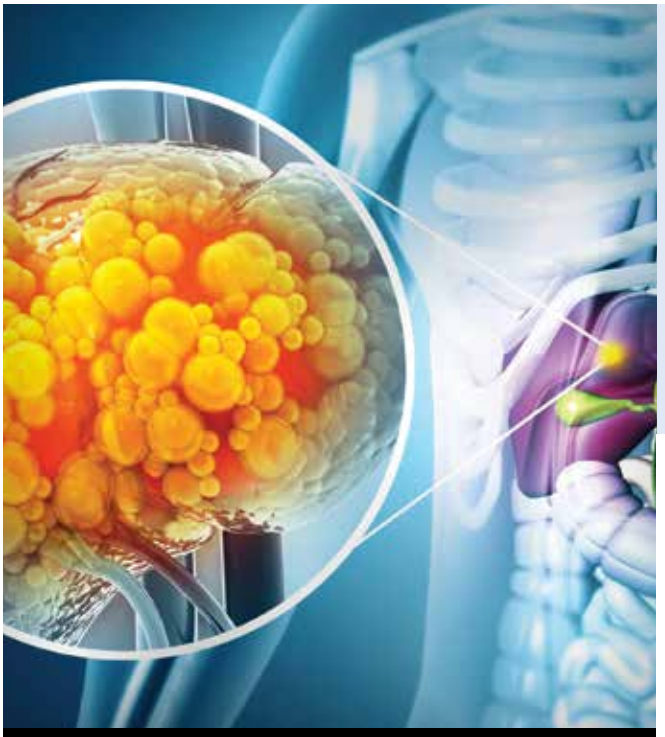

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ENDOCRINE SOCIETY

Hormone Science to Health

Laureate Awards Showcase Our Field's Top Talent

The prestigious endocrine researchers and clinicians honored with our 2024 Laureate Awards represent the best and brightest in our field.

Our Laureate Award winners also demonstrate the way endocrinology and the Endocrine Society transcend borders. The honorees hail from six countries and four continents. We are proud to recognize outstanding researchers and clinicians from Argentina, Brazil, France, India, the United Kingdom, and the United States.

The winners are committed to caring for diverse populations. Vigersky Outstanding Clinical Practitioner Award winner Sandra Daniela Licht, MD, travels to rural Patagonia in Argentina to treat individuals who would otherwise have limited access to care. Outstanding Educator Award winner A. Enrique Caballero, MD — a member of our Committee on Diversity and Inclusion — established programs to provide diabetes care to the Latino community at Joslin Diabetes Center and Brigham & Women's Hospital.

Our Laureate Award winners also include individuals who are working to expand and diversify our endocrine workforce. Past-president E. Dale Abel, MBBS, MD, PhD, is the deserving recipient of our Fred Conrad Koch Lifetime Achievement Award. In addition to his seminal work researching heart complications of obesity and insulin resistance, Abel has mentored professionals at the University of California, Los Angeles, and the University of Iowa, and has spearheaded our Future Leaders Advancing Research in Endocrinology (FLARE) program. For more than a decade, FLARE has nurtured the research career aspirations of individuals from underrepresented minorities.

In fact, as an example of the success of the FLARE program, one of the first FLARE fellows, Joshua J. Joseph, MD, MPH, of the Ohio State University College of Medicine, is the recipient of the Richard E. Weitzman Outstanding Early Career Investigator Award. Joseph is seeking to identify obesity and type 2 diabetes risk factors in diverse populations and opportunities for prevention.

Outstanding Mentor Award winner Sanjay Bhadada, MD, DM, has helped guide and shape the careers of dozens of young professionals in his role as professor of endocrinology and head of the Endocrinology Department at the Postgraduate Institute of Medical Education and Research in Chandigarh, India. His mentees have gone on to become leaders and heads of departments in medical schools in India as well as elsewhere in Southeast Asia, the United States, and Europe.

The 2024 Laureate Award winners also are breaking new ground in the research world. Morris Brown, MD, has made amazing contributions toward our understanding of underrecognized adrenal causes of hypertension. His pioneering translational work is being acknowledged with the Gerald D. Aurbach Award for Outstanding Translational Research.

We are proud to honor Vincent Prevot, PhD, with the Edwin B. Astwood Award for Outstanding Research in Basic Science. As the research director and laboratory head of development and plasticity of the neuroendocrine brain at Lille Neuroscience & Cognition, Inserm in Lille, France, Prevot's research into the neuronal and glial plasticity in the GnRH system has advanced our understanding of the onset of puberty and adult fertility.

Our winners are leading the way in translating lab discoveries into public health innovations. Outstanding Leadership in Endocrinology Award winner Anne Klibanski, MD, PhD, is overseeing growing investment in leading-edge research that has the potential to revolutionize treatments, such as gene and

cell therapy. She is president and chief executive officer of Mass General Brigham and chief of the Neuroendocrine Unit at the Massachusetts General Hospital in Boston, Mass. The system's innovation team has created more than 300 companies that are making broad impacts on human health.

Outstanding Innovation Award winner David Katz, PhD, is the founder and chief scientific officer of Sparrow Pharmaceuticals, Inc., in Portland, Ore. Katz and his team developed a novel therapy, the HSD-1 inhibitor SPI-62. The prospect of a long-awaited new treatment option for Cushing's syndrome is thrilling.

Our honorees are developing better solutions to the obesity epidemic. Outstanding Clinical Investigator Award winner Sadaf Farooqi, MD, PhD, of the University of Cambridge, discovered the first genes whose disruption causes severe obesity and established that the failure of central control of appetite is the principal driver of obesity. Evan D. Rosen, MD, PhD, winner of the Roy O. Greep Award for Outstanding Research, is researching the transcriptional pathways that underlie metabolic disease. His lab at Beth Israel Deaconess Medical Center in Boston, Mass., created many mouse models that are widely used to study adipose tissue.

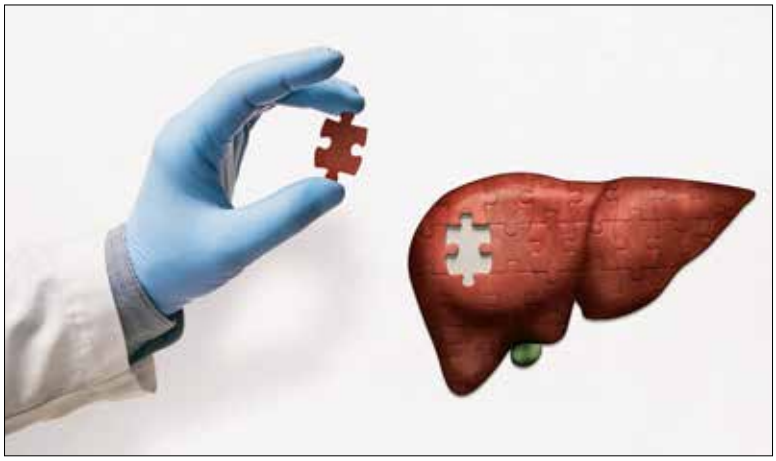
Rounding out the 2024 Laureate honorees are dedicated Society volunteers Past-President Lynnette Nieman, MD, Dolores Shoback, MD (my fellowship program director and amazing mentor at UCSF!), and Cesar Boguszewski, MD, PhD. All three have served on our Board of Directors and numerous committees. Their commitment has helped shape the Endocrine Society into a warm and welcoming community for all endocrine professionals.

If you would like to see a colleague's achievements recognized, be sure to nominate them for a 2025 Laureate Award. We are already accepting nominations on our website.

As you cross paths with our Laureate winners, be sure to congratulate them. I can't wait to honor this impressive group when we meet in Boston, Mass., for **ENDO 2024**.

Stephen R. Hammes, MD, PhD
President, Endocrine Society

Liver Steatosis and the Endocrinologist



This month's issue is an unusual one for us as it focuses on a malady that we seldom focus on in *Endocrine News*, much less devote an entire issue to it: steatotic liver disease. Since this condition is destined to reach epidemic proportions along with obesity and diabetes, we felt this was a good time to give it a closer look.

In **"Hepatic Helpers: Endocrinology in the Age of Heightened Liver Disease"** on page 40, senior editor Derek Bagley looks at recent studies published in *The Journal of Clinical Endocrinology & Metabolism* that really highlight the unique opportunity that will be coming endocrinologists' way in playing a major role in managing nonalcoholic liver disease along with its many comorbidities. As noted in the article, since there are no FDA-approved treatments for liver disease, endocrinologists can step in not only by caring for these patients, but in pursuing relevant research. "We have data that's unpublished, that shows that people who attend endocrine clinics have twice the rate of advanced liver fibrosis and cirrhosis than in primary care," says Kenneth Cusi, MD, chief, Division of Endocrinology, Diabetes and Metabolism at the University of Florida, Gainesville, Fla., adding that "because of that, we have a greater responsibility of identifying them, so they can be co-managed with hepatology and given a formal diagnosis, and some interventions that can be implemented today."

On page 20, Eric Seaborg looks at a multi-session program that was featured at **ENDO 2023** in Chicago in **"Endocrine Targets: Taking the Lead in**

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Executive Editor: **Mark A. Newman**
mnewman@endocrine.org

Senior Editor: **Derek Bagley**
dbagley@endocrine.org

Art Director/Production: **Anthony S. Picco**

Art Director/Design: **Catherine C. Neill, CNJ Creative, saLLC**
www.cnjcreative.com

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Treating Steatotic Liver Disease." Eric notes in his article that the session was planned in order to raise endocrinologists' awareness of their potential roles in addressing endocrine targets in steatotic liver disease "and as a reflection of attendees' interest, the room had to be enlarged to accommodate all those who wished to attend," he writes. Also included in the piece is a sidebar about the nomenclature adjustment for the various disorders so that the descriptions would be less stigmatizing going forward. Laura E. Dichtel, MD, MHS, of Harvard Medical School and Massachusetts General Hospital, was one of the **ENDO 2023** speakers was not involved in these updates, but she says that the "new terminology has already begun to be adopted and will hopefully support advances in research and clinical care by defining steatotic liver disease more precisely."

In **"Guilt by Association: Exploring the Concerning Links Among NASH, MAFLD, Diabetes, and Obesity"** on page 28, Derek conducts a Q&A with Theodore C. Friedman, MD, PhD, MPH, MS, and Magda Shaheen, MD, PhD, of Charles R. Drew University of Medicine & Science, about research they presented at **ENDO 2023** that further details fatty liver disease's link to diabetes, what impact new medications could have, and their views on how endocrinologists can help stem the tide. According to Friedman, diabetes clearly leads to more liver disease because "the higher the A1c, the more fatty liver disease," he says, but adds his team performed correlations and he can't say for certain that the reverse is true that "more severe liver disease leads to more diabetes. I think it's clear diabetes and pre-diabetes lead to fatty liver disease."

Please feel free to let us know what you think of this narrowly focused issue highlighting endocrinology's role in managing and seeking treatments for steatotic liver disease. As always, I welcome your comments and suggestions at: **mnewman@endocrine.org**

— **Mark A. Newman**, Executive Editor, *Endocrine News*

ENDO 2023 SESSION RECORDINGS

VIEW MORE THAN 150 SESSIONS AND EARN UP TO 110 CME CREDITS

PURCHASE TODAY

ENDOCRINE SOCIETY

BY DEREK BAGLEY
Senior Editor

New Research Points to Potential Drug Targets to Treat Pelvic Pain in Endometriosis

Researchers have discovered potential pathways that can lead to novel therapeutic drug targets to treat inflammation and nociception associated with endometriosis, according to a paper recently published in the *American Journal of Pathology*. Pelvic pain in women with endometriosis is attributed to neuroinflammation. Researchers investigated biochemical mediators of endometriosis-associated pelvic pain to provide a foundation to identify new drugs to improve symptoms and quality of life.

Researchers led by Robert N. Taylor, MD, PhD, Departments of Obstetrics and Gynecology and of Pathology and Anatomical Sciences, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, postulated that novel therapeutic targets for pelvic pain in endometriosis are regulated by interleukin-1β (IL-1β) via the c-Jun N-terminal kinase (JNK) signaling pathway. IL-1β has been a popular focus of translational research in the field of endometriosis.

"Endometriosis is common and complex and likely to develop via multiple etiological mechanisms," Taylor says. "As a result, multiple therapeutic targets are needed. Strategies over the past five decades have focused on surgical and endocrine approaches. New drugs aimed to block neuroinflammation may be promising future interventions for endometriosis-associated pain."

This collaborative research effort sought to identify biochemical mediators of endometriosis-associated pelvic pain using established neural biomarkers isolated from endometrial tissue biopsies obtained from eight adult women undergoing hysterectomy (four patients with endometriosis; four without).

Immunofluorescence histochemistry confirmed the presence of neurons in human endometrial tissue, and isolated endometrial stromal cells (ESCs) expressed neurotrophins and their receptors. Peritoneal fluid samples were analyzed from 14 participants with and 26 participants without endometriosis.

Tropomyosin receptor kinase A/B (TrkA/B) expression in stimulated ESCs was almost twice as high in endometriosis cases than ESCs from control subjects, an effect mediated via the c-Jun N-terminal kinase (JNK) pathway. Investigators therefore postulate that JNK inhibitors have the potential to reduce neuroinflammation in women with endometriosis.

Nerve fibers were identified in the human uterus more than 80 years ago, but only in the past decade has their association with endometriosis pain been appreciated. The main findings of this study are that despite functioning through at least five different post-receptor signal cascades, the IL-1β pathway in ESC that engages JNK regulates a coordinated program of neurogenic factors, their receptors and other related nerve proteins that investigators identified in the uterus and ectopic lesions of women with endometriosis. They also found that JNK inhibitors may have the potential to reduce neuroinflammation in women with endometriosis.

The results revealed that many of the dominant mediators of inflammation, nerve growth, and pain sensation are predominantly communicated via a selective signaling node of the JNK pathway. The most significant implication of this finding is the potential for drugs targeting that common pathway to impact and ameliorate the multifaceted aspects of endometriosis-associated pelvic pain.

"Endometriosis is common and complex and likely to develop via multiple etiological mechanisms. As a result, multiple therapeutic targets are needed. Strategies over the past five decades have focused on surgical and endocrine approaches."

> While obesity associated with PCOS may increase the risk of diabetes, hypertension, and other health problems, obesity does not appear to increase the risk of developing PCOS.

Obesity Does Not Appear to Increase the Risk of Developing PCOS

Obesity does not appear to increase the risk of developing polycystic ovary syndrome (PCOS), according to a study presented at **ENDO 2023**.

The researchers point out that PCOS is a complex genetic trait and the most common endocrine disorder of women, with significant cardio-metabolic and reproductive morbidities. "PCOS is clinically evident in 5% – 15% of all reproductive-aged women globally," the authors write.

Women with PCOS have a hormonal imbalance and metabolism problems that may affect their overall health, appearance, and fertility. PCOS is associated with health issues including:

- Acne, scalp hair loss, and excessive hair growth;
- Increased risk of infertility;
- Increased risk of diabetes, metabolic syndrome, and hypertension;
- Increased risk of depression, anxiety, and eating disorders; and
- Increased risk of endometrial cancer.

Obesity has been viewed as driving the high prevalence of PCOS, the single most common endocrine disorder of women.

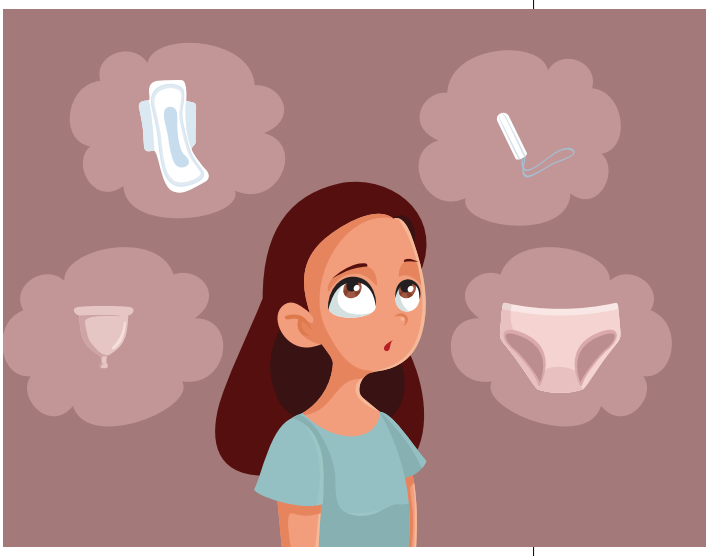
"Our study suggests for the first time that the high prevalence of PCOS in the world is due to factors other than the rising obesity rate globally," says Mina Amiri, PhD, of Shahid Beheshti University of Medical Sciences in Tehran, Iran, who is one of the study's authors. "While obesity associated with PCOS may increase the risk of diabetes, hypertension, and other health problems, obesity does not appear to increase the risk of developing PCOS."

The researchers evaluated 54 studies, including 78,592 women of reproductive age, which recorded the prevalence of PCOS globally. They compared the prevalence of PCOS with the prevalence of obesity in individual populations. They found no significant associations between the obesity prevalence in a population and its PCOS prevalence.

"The findings of the research may help clinicians and the general public understand that obesity and PCOS do not go hand-in-hand and that many women with PCOS are not obese," says senior author Ricardo Azziz, MD, MPH, MBA, of the University of Alabama at Birmingham.

More Girls Started Puberty Early During the COVID-19 Pandemic

The number of girls diagnosed with precocious puberty increased during the COVID-19 pandemic due to potential risk factors such as increased screen time and less physical activity, according to a new study published in the *Journal of the Endocrine Society*. The number of girls referred to pediatric endocrinologists for precocious puberty has increased significantly over the past two years, potentially due to the COVID-19 pandemic.



COVID-19 has also been linked to endocrine diseases such as obesity, which is a known contributor to early puberty in girls.

"Our study confirms the rise in precocious puberty diagnoses during COVID-19 and identifies contributing factors such as poor eating and exercise habits, too much screen time, and impaired sleep," says study author Mohamad Maghnie, MD, PhD, of the University of Genoa and the Giannina Gaslini Institute in Genoa, Italy. "We found an increase in weight gain among girls diagnosed with precocious puberty during the pandemic, and rapid increase in body weight is associated with advanced pubertal development."

The researchers evaluated the incidence of precocious puberty before and after the COVID-19 pandemic in 133 girls from Italy. They also examined the possible relationship between COVID-19 and pandemic-related lifestyle changes.

They found 72 cases of precocious puberty before the COVID-19 pandemic (January 2016 – March 2020) and 61 cases between March 2020 and June 2021. That equates to four new cases per month.

The researchers also found girls diagnosed with precocious puberty during the COVID-19 pandemic tended to have higher body mass index (BMI) scores than girls who did not. These girls spent an average of two hours per day using electronic devices, and 88.5% of them stopped any physical activity.

"The role of stress, social isolation, increased conflicts between parents, economic status, and the increased use of hand and surface sanitizers represent potentially further interesting hypotheses as to why early puberty is increasing in youth," Maghnie says. "Although, the consequence of biological adaptation cannot be entirely ruled out." EN

> **"Our study confirms the rise in precocious puberty diagnoses during COVID-19 and identifies contributing factors such as poor eating and exercise habits, too much screen time, and impaired sleep."**

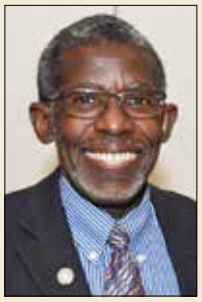
Meet the 2024 Endocrine Society Laureates

On August 17, the Endocrine Society announced 14 leading endocrinologists as winners of its prestigious 2024 Laureate Awards, the top honors in the field.

These professionals have achieved breakthroughs in scientific discoveries and clinical care benefiting people with hundreds of conditions, including diabetes, thyroid disorders, obesity, hormone-related cancers, growth problems, osteoporosis, and infertility.

Established in 1944, the Society's Laureate Awards recognize the highest achievements in the endocrinology field, including groundbreaking research and innovations in clinical care. The Endocrine Society will present the awards to the winners at **ENDO 2024**, the Society's annual meeting in Boston, Mass., June 1 – 4, 2024.

The Endocrine Society's 2024 Laureate Award winners are:



E. Dale Abel, MBBS, DPhil

Fred Conrad Koch Lifetime Achievement Award

The Society's highest honor, this annual award recognizes lifetime achievements and exceptional contributions to the field of endocrinology. Abel is a past-president of the Endocrine Society and the current chair and executive medical director of the Department of Medicine at the University of California, Los Angeles (UCLA) and UCLA Health in Los Angeles, Calif. He has a lengthy record as a researcher and clinician, and as a mentor to young scientists. Abel's pioneering work on glucose transport and mitochondrial metabolism in the heart guided his research interest in molecular mechanisms responsible for cardiovascular complications of diabetes. His laboratory has provided important insights into the contribution of mitochondrial dysfunction and aberrant insulin signaling to heart failure risk in diabetes. His research has been continually funded by the National Institutes of Health (NIH) for more than 20 years, and his scientific contributions have been recognized by election to the National Academy of Medicine and the National Academy of Sciences in the United States. He previously served as the chair and executive officer of the Department of Internal Medicine and professor of medicine, biochemistry, and biomedical engineering at the University of Iowa in Iowa City, Iowa. Since 2012, he has been a principal investigator for the Endocrine Society's Future Leaders Advancing Research in Endocrinology (FLARE) program, which has helped individuals from underrepresented groups establish successful careers in endocrinology and diabetes research. He has held several leadership positions at the Endocrine Society, including past-president, and is currently a deputy editor for *Endocrine Reviews*.

Morris Brown, MA, MSc, MD

Gerald D. Aurbach Award for Outstanding Translational Research

This annual award recognizes outstanding contributions to research that accelerates the transition of scientific discoveries into clinical applications. Brown is the professor of endocrine hypertension at Queen Mary University of London in London, United Kingdom. His research focuses on finding adrenal causes of hypertension and the right treatment for the right patient. In 1999, he proposed the AB/CD rule, which underpins many guidelines for hypertension. As president of the British Hypertension Society, he conducted the "PATHWAY" clinical trials to establish optimal treatment for different categories of hypertension. His current research is mainly focused on the adrenal gland and the small aldosterone-producing adenomas that are a common cause of hypertension and are unrecognized in 99% of cases. Morris' pioneering translational work fulfills his vision to identify and appropriately treat all patients with aldosterone-related hypertension, thereby revolutionizing patient care and long-term outcomes.

Vincent Prevot, PhD

Edwin B. Astwood Award for Outstanding Research in Basic Science

Originally awarded from 1967 and renamed to honor the scientific contributions of the late Edwin B. Astwood, MD, this award recognizes individuals who have made significant contributions to the field of endocrinology via their outstanding basic science research. Prevot is a research director at Inserm (French National Institute of Health and Medical Research) and laboratory head of development and plasticity of the neuroendocrine brain at Lille Neuroscience and Cognition, France. His research into neuronal and glial plasticity in the GnRH system is crucial for understanding the onset of puberty and adult fertility. He has provided many seminal contributions and groundbreaking concepts in the understanding of the central control of mammalian reproduction. His current research focuses on neuroscience and neuroendocrinology, in particular the brain circuits that control reproduction and metabolism and the neural pathways through which they respond to peripheral information. He served as an editorial board member of the Endocrine Society journal, *Endocrinology*.

Cesar Luiz Boguszewski, MD, PhD

International Excellence in Endocrinology Award

This award is presented to an endocrinologist who has made exceptional contributions to the field in geographic areas with underdeveloped resources for hormone health research, education, clinical practice, or administration. Boguszewski is a full professor of endocrinology and metabolism in the Department of Internal Medicine at the Federal University of Paraná in Curitiba, Brazil, where he founded SEMPR — the Endocrine Division of the University Hospital. He is currently the head of SEMPR and director of the Neuroendocrinology Unit within the University Hospital. He was the president of the Brazilian Society of Endocrinology and Metabolism (SBEM) during the 2021 – 2022 term, and now he coordinates the SBEM International Committee. He has served on several Endocrine Society committees, most recently as a member of the Board of Directors, Governance Task Force, Trainee and Career Development Core Committee, and CEO Search Committee. He was associate editor of the *European Journal of Endocrinology* for eight years and is now associate editor of *Reviews in Endocrine and Metabolic Disorders* and *Endocrine*. His main fields of interest are pituitary diseases, obesity and neuroendocrine regulation of body weight, and body composition. He has authored more than 150 journal articles and book chapters, and co-edited a medical book entitled *Pituitary: The Master Gland*.

Sadaf Farooqi, MD, PhD

Outstanding Clinical Investigator Award

This annual award honors an internationally recognized clinical investigator who has contributed significantly to understanding the pathogenesis and therapy of endocrine and metabolic diseases. As a clinical scientist and professor of metabolism and medicine at the

Wellcome–MRC Institute of Metabolic Science at the University of Cambridge in Cambridge, U.K., Farooqi researches the fundamental mechanisms that control human energy homeostasis. She discovered the first genes whose disruption causes severe obesity and established that the principal driver of obesity is a failure of the central control of appetite. In children with congenital leptin deficiency treated with recombinant leptin, she showed that leptin reduced hyperphagia, permitted the onset of puberty at an appropriate developmental stage, and reversed T cell mediated immune dysfunction. She has held roles within the Endocrine Society, including associate editor of *The Journal of Clinical Endocrinology & Metabolism* and member of the Society's Annual Meeting Steering Committee. Farooqi also participates in advocacy efforts to raise more awareness around weight stigma and obesity as a disease.

Sandra Daniela Licht, MD

Vigersky Outstanding Clinical Practitioner Award

This annual award recognizes extraordinary contributions by a practicing endocrinologist to the endocrine and/or medical community. Licht has been a clinical endocrinologist at her private practice in Buenos Aires, Argentina, for over 25 years. Her expertise is thyroid disease. She sees more than 100 patients per week at her office and makes the time to travel 1,000 miles every other month to provide endocrine care to an underserved rural population in remote Patagonia. She also shares her expertise by lecturing to medical and patient groups throughout South America. For the past 15 years, she has been a medical advisor to the Association of Patients with Thyroid Cancer of the Argentina Republic and a member of the Medical Advisory Panel of the Thyroid Cancer Alliance, an international network of national thyroid cancer support groups. She is currently a member of the Endocrine Society's Nominating Committee and has served on the Clinical Practice Guidelines and Publication Core Committees.

A. Enrique Caballero, MD

Outstanding Educator Award

This annual award recognizes exceptional achievement as an educator in the discipline of endocrinology and metabolism. Caballero is the director of International Innovation Programs in the Office for External Education and the director of diabetes education in the Postgraduate Medical Education Department at Harvard Medical School in Boston, Mass. He also is the director of Latino Diabetes Health and an associate scientist at the Brigham & Women's Hospital in Boston, Mass. He founded the Latino Diabetes Initiative at the Joslin Diabetes Center and the Diabetes Program within the Spanish Clinic at the Brigham & Women's Hospital. His research interests include type 2 diabetes and cardiovascular disease prevention as well as management of diabetes in racial/ethnic minorities, particularly the Latino/Hispanic population. He has worked in the field of diabetes education for over two decades and is a well-recognized leader at a national and international level, and a prominent figure in the field of diabetes in underserved communities. He has trained dozens of medical students, residents, fellows, researchers, allied health professionals, and physicians from the U.S., Latin America, and Spain on the complex challenge of managing diabetes in underserved communities. He currently serves on the Endocrine Society's Committee on Diversity & Inclusion.

Anne Klibanski, MD, PhD

Outstanding Leadership in Endocrinology Award

This annual award recognizes outstanding leadership in fundamental or clinical endocrinology. Klibanski is president and CEO of Mass General Brigham in Boston, Mass. She served as the healthcare system's chief academic officer from 2012 to 2019 and as chief of neuroendocrine at Massachusetts General Hospital. Mass General Brigham is the largest hospital-based research enterprise in the U.S., with annual funding of more than $2 billion. Klibanski leads clinical integration of services across Mass General Brigham and is responsible for the development of new digital platforms to achieve virtual care. She oversees increased investment in leading-edge research that has the potential to revolutionize

treatments, such as gene and cell therapy. The system's innovation team has created more than 300 companies that are making broad impacts on human health, in various spaces — from therapeutics to diagnostics and research. Under Klibanski's leadership, Mass General Brigham has committed significant resources to community health, with a particular investment in mental health programs. She established "United Against Racism," a long-term, multi-year commitment to address the impacts that racism has on Mass General Brigham patients, employees, and the broader community. She is recognized internationally for her high-impact research in neuroendocrine disorders and pituitary tumors.

Sanjay Bhadada, MD, DM
Outstanding Mentor Award

This annual award recognizes a career commitment to mentoring and a significant positive impact on mentees' education and career. Bhadada is a professor of endocrinology and head of the Endocrinology Department at the Postgraduate Institute of Medical Education and Research in Chandigarh, India. He established one of the most highly sought-after postgraduate training programs in endocrinology in Southeast Asia and has mentored more than 40 endocrinology fellows and medical students, numerous graduate students and postdoctoral fellows, and many early-career faculty. As the current president of the Endocrine Society of India and as former secretary of the Indian Society of Bone Mineral Research, he has provided outstanding leadership in expanding the training and educational venues for fellows and medical students at a national level. He is currently an editorial board member for *The Journal of Clinical Endocrinology & Metabolism*.

David Katz, PhD
Outstanding Innovation Award

Established in 2013, this award is presented to recognize an individual or team of people who have demonstrated innovation to further endocrine research or practice in support of the field of endocrinology, patients, and society at large. Katz is the founder and chief scientific officer of Sparrow Pharmaceuticals, Inc., in Portland, Ore., a pharmaceutical company developing targeted therapies for conditions of cortisol excess and to reduce the side effects of glucocorticoid medicines. Prior to Sparrow, Katz was a leader in personalized medicine, drug discovery, and clinical development at Abbott and AbbVie. Katz and his team developed a novel therapy, the HSD-1 inhibitor SPI-62, that is currently in Phase 2 clinical trials for treating Cushing's syndrome, autonomous cortisol secretion (ACS), and, in combination with prednisolone, polymyalgia rheumatica. The current therapies for treating these conditions are not always both effective and safe. SPI-62 could be the first novel-mechanism drug in over 30 years for people with Cushing's.

Dolores Shoback, MD
Outstanding Scholarly Physician Award

This annual award recognizes outstanding contributions to the practice of clinical endocrinology in academic settings. Shoback cares for patients who have endocrine disorders such as metabolic bone disease, parathyroid disorders, and osteoporosis at the San Francisco Veteran Affairs Medical Center and the University of California, San Francisco (UCSF). She is also the associate program director of UCSF's physician training program in diabetes, endocrinology, and metabolism. Shoback's research interests include metabolic bone disease, the calcium-sensing receptor, and parathyroid hormone. Shoback is a basic and clinical investigator who has made immense contributions to our understanding of metabolic bone diseases. She has been an effective educator of physicians and patients for three decades. Since becoming an Endocrine Society member in 1987, she has held several service positions, including secretary-treasurer of its Board of Directors and chair of the Finance and Audit Committee. She served as the co-chair of *The Journal of Clinical Endocrinology & Metabolism* Working Group, a member of the Editor-in-Chief Search Committee for *Endocrinology*, and a member of the Osteoporosis Clinical Practice Guideline Writing Committee.

Joshua J. Joseph, MD, MPH
Richard E. Weitzman Outstanding Early Career Investigator Award

This annual award recognizes an exceptionally promising young clinical or basic investigator. Joseph is an associate professor of medicine at The Ohio State University Wexner Medical Center and

College of Medicine in Columbus, Ohio. He is an exceptional young investigator who translates hypothesis-generating population science findings into clinical and community-based interventions. Joseph's research focus is to understand risk factors for the development of obesity and type 2 diabetes in diverse populations. He has been working to shed light on racial and ethnic differences in the association of physical activity and other lifestyle factors in the development of diabetes using large multi-ethnic observational cohorts, including the Multi-Ethnic Study of Atherosclerosis (MESA) and the Jackson Heart Study. He uses this data to design and execute detailed metabolic clinical studies to uncover explanatory mechanisms as potential targets for preventive interventions for diabetes and obesity. He currently serves as chair of the Society's Clinical Affairs Core Committee.

Evan D. Rosen, MD, PhD

Roy O. Greep Award for Outstanding Research

This annual award recognizes meritorious contributions to research in endocrinology. As chief of the Division of Endocrinology, Diabetes, and Metabolism at Beth Israel Deaconess Medical Center and professor of medicine at Harvard Medical School in Boston, Mass., and an institute member of the Broad Institute in Cambridge, Mass., Rosen has made unique and important contributions to our understanding of adipose biology. His lab's goal is to define novel targets that can be manipulated to improve outcomes in metabolic disease. They research the transcriptional pathways that underlie metabolic diseases like obesity and type 2 diabetes. They use genomic and epigenomic approaches to identify novel transcription factors and pathways that regulate processes such as adipogenesis, lipid handling, insulin resistance, and metabolic memory. His lab also created many mouse models that are widely used by the research community to study adipose tissue. Rosen has authored several very prominent reviews on adipose biology, which have collectively been cited more than 7,000 times. He is a former editorial board member for the Society's basic science journal, *Endocrinology*.

Lynnette Nieman, MD

Sidney H. Ingbar Distinguished Service Award

This award recognizes distinguished service to the Endocrine Society and the field of endocrinology. Nieman is a senior investigator at the National Institutes of Health (NIH), where she served as the associate program director of the Inter-Institute Endocrinology Training Program for 12 years and is currently chief of the Adult Endocrinology Consult Service. Her research focus is adrenal gland disorders and disorders of female reproduction. She has contributed to the diagnosis and differential diagnosis of Cushing's syndrome and Phase II/III studies of ulipristol acetate leading to the European Medicines Agency's (EMA) approval for the treatment of fibroids and the U.S. Food and Drug Administration and the EMA's approval for emergency contraception. For over 25 years, she has held leadership positions at the Endocrine Society, most notably as Society President in 2017 – 2018. During her presidency, she led the Strategic Plan and Governance Task forces that created the Endocrine Society's current fourth Strategic Plan and revised its governance structure. She has served on numerous committees, including chairing the Annual Meeting Steering Committee and the Clinical Endocrinology Update Committee. She was a member of the Nominating Committee, the Publications Core Committee, and the Research Affairs Core Committee. She was also an associate editor of T*he Journal of Clinical Endocrinology & Metabolism*. She is currently the chair of the Society's Clinical Practice Guideline Task Forces for the diagnosis and treatment of Cushing's syndrome.

Nominations are being accepted for the 2025 Laureate Awards cycle until Friday, January 20, 2024. Any submissions received after January 20 will be considered for the following year.

Remembering Richard D. Gordon, AO, MD, PhD, 1934 – 2023

BY MICHAEL STOWASSER, MBBS, FRACP, PHD

It is with great sadness that we say farewell to Richard D. Gordon, an Australian pioneer of endocrinology and hypertension research, who recently passed away after a brief illness, age 89.

Born in Brisbane, Gordon's training as an endocrinologist included research fellowships in Melbourne (Bryan Hudson, The Alfred and Prince Henry's Hospitals, Monash University), Nashville, Tenn. (Vanderbilt University) under the inspirational Grant Liddle (Liddle's syndrome, leading authority on the adrenal gland), and the University of Adelaide (Basil Hetzel). In addition to clinical work, these fellowships heavily involved laboratory bench work, setting up, validating, and trouble-shooting new assays, which added an invaluable dimension to his critical judgement and expertise as a clinical scientist.

Following these fellowships, Gordon returned to Brisbane in 1970 to head the new section of the University of Queensland (UQ) Department of Medicine at Greenslopes Hospital. He established endocrine units at Greenslopes and Princess Alexandra Hospitals and a Hypertension Unit at Greenslopes Hospital, which developed into an Endocrine Hypertension Research Centre. He accepted a personal chair in Medicine at UQ in 1982. The Greenslopes Unit achieved a reputation for meticulous diagnostic procedures, attracting referrals from throughout Queensland and other Australian centers.

Gordon painstakingly developed strict protocols for the diagnosis and management of primary aldosteronism that are still widely regarded as best practice today. He correctly predicted in 1992 (*Lancet*) that primary aldosteronism would often have a genetic basis.

Gordon published around 300 scientific papers in peer-reviewed journals, and 24 chapters in texts. He completed an MD thesis (1966) entitled "Circadian rhythms in man. A transverse study of some temporal aspects of adrenocortical and renal function" and a PhD thesis (1981) entitled "Systemic arterial hypertension: adrenocorticotrophin and aldosterone in pathophysiology."

Gordon was made an Officer in the General Division of the Order of Australia (AO) for services to medicine in the field of endocrine causes of hypertension in 1994.

With his many contributions to medicine and science, Gordon has truly earned the right to be recognized as a pioneer in all facets of hypertension, whether research, clinical practice, or public awareness and education. He is survived by his wife Susan, daughters Susan, Sara-jane, and Christina, and son Michael.

– Stowasser is the director of the Hypertension Unit and the Endocrine Hypertension Research Centre at the University of Queensland Frazer Institute at the Princess Alexandra Hospital in Brisbane, Australia. He is also the editor-in-chief of the Journal of Human Hypertension.

MEMBERS in the NEWS

Madhusmita Misra, MD, MPH, Named Pediatrics Chair at UVA

Madhusmita Misra, MD, MPH

The University of Virginia School of Medicine has named Endocrine Society member Madhusmita Misra, MD, MPH, chair of its Department of Pediatrics and who will serve as physician-in-chief for UVA Health Children's.

Misra comes to UVA from Massachusetts General Hospital and Harvard Medical School in Boston, where she served as chief of the Division of Pediatric Endocrinology. She is also the director of pediatric research and associate program director at the Massachusetts General Hospital Translational and Clinical Research Center, medical research officer at Massachusetts General Hospital, and associate chief for academic faculty development at Mass General for Children.

Misra has more than 15 years of leadership experience at Massachusetts General Hospital and Harvard Medical School, where she has also served as the fellowship program director for pediatric endocrinology, clinical director for the Division of Pediatric Endocrinology, and co-chair of the faculty development program at Mass General for Children. At the national level, she has held several leadership roles, including that of president of the Pediatric Endocrine Society.

Her research efforts include serving as director of the Pediatric Endocrine-Neuroendocrine-Sports Endocrine Laboratory at Massachusetts General Hospital. Misra's research has focused on how weight-related conditions from anorexia to obesity affect bones and the body's hormone system, and her findings have had a significant impact on the management of low bone density in youth with low-weight eating disorders. She has published more than 200 peer-reviewed original research papers and has co-edited two pediatric endocrine textbooks. Misra has been continuously funded by the National Institutes of Health (NIH) and other funding agencies for her research since 2004, and currently serves as principal investigator or multi-principal investigator on three NIH R01 grants and a Department of Defense grant.

As a clinician, Misra specializes in caring for children with neuroendocrine and bone disorders. During her tenure as chief for the Division of Pediatric Endocrinology, she developed several specialty programs, including a multidisciplinary pediatric diabetes program at Mass General for Children that provides comprehensive care for children with type 1 and type 2 diabetes and their families and expanded the division's outreach efforts to serve patients at 10 satellite clinic locations.

Misra earned her medical degree from S.C.B. Medical College at Utkal University in India and a master's degree in public health from the Harvard School of Public Health. After completing an internship at S.C.B. Medical College and a residency in obstetrics and gynecology at the Institute of Medical Sciences in Varanasi, India, she went on to complete a residency in pediatrics at Maimonides Medical Center in New York and a fellowship in pediatric endocrinology at Massachusetts General Hospital.

"I am delighted and deeply honored to serve as the next chair of the Department of Pediatrics at UVA and physician-in-chief of UVA Children's Hospital," Misra says. "It will be my privilege to serve in these roles and to work with current leadership to take the department and the children's hospital to the next level." EN

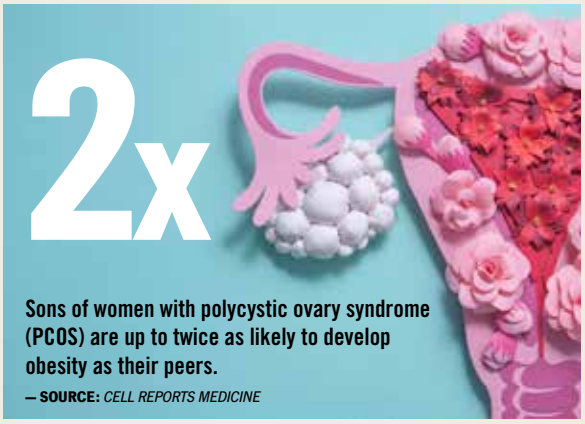
> Endocrinologists should take a lead in treating MASLD because the increase in incidence of this disorder is in large part driven by metabolic factors. In treating the root causes of MASLD, endocrinologists can have a significant impact on the incidence, prevalence, and morbidity of the disorder. **For similar reasons, we should also take a lead in research in this area. We can and should identify metabolic and endocrine therapeutic targets and test potential new treatments for MASLD."**

– Karen Klahr Miller, MD, professor of medicine, Harvard Medical School; chief, Neuroendocrine Unit, Massachusetts General Hospital, Boston, Mass., discussing how important the role of the endocrinologist will be moving forward in treating steatotic liver disease in **"Endocrine Targets: Taking the Lead in Treating Steatotic Liver Disease"** on page 20.

42%

The percentage of women in early perimenopause who will lose a significant fraction of peak bone mass within two to three years.

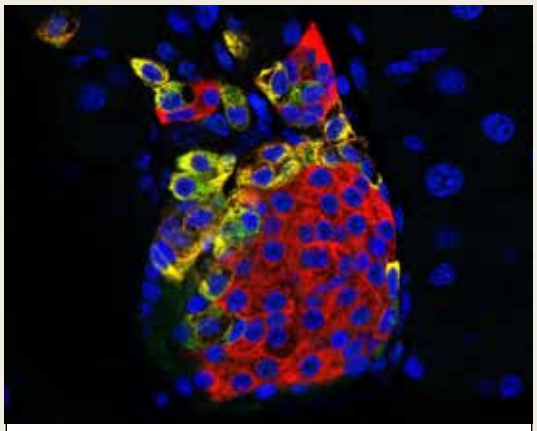
– SOURCE: *JOURNAL OF BONE AND MINERAL RESEARCH*



2x

Sons of women with polycystic ovary syndrome (PCOS) are up to twice as likely to develop obesity as their peers.

– SOURCE: *CELL REPORTS MEDICINE*



Endocrine Image of the Month

Rachel Reinert, PhD, MD, an assistant professor at the University of Michigan in Ann Arbor, asks "Whooo is ready to learn about prohormone processing?" in this image from the Endocrine Society's 2023 Endocrine Images Art Competition that shows how pancreatic islets can make fun shapes under the microscope, like this one mimicking a perched horned owl. "These islet cells were labeled for glucagon (green) and the processing enzyme prohormone convertase 2 (PC2, red) in addition to the nuclear stain DAPI (blue)," she explains.

1.3 billion

The number of people worldwide with diabetes is projected to more than double in the next three decades, reaching 1.3 billion by 2050.

– SOURCE: *LANCET*

2x

Patients with early-stage breast cancer who do not adhere to adjuvant endocrine therapy as prescribed or stop early may face as much as a two times higher risk of relapse or death, a new systematic review found.

– SOURCE: *BMC CANCER*

2023 Endocrine Board Review/Clinical Endocrinology Update

EBR 2023
ENDOCRINE BOARD REVIEW

Sept. 8 – 10, 2023/Virtual Only

Endocrine Board Review (EBR) 2023 is the leading online training program for fellows, residents, and physicians preparing for board certification exams. EBR's comprehensive curriculum will ensure you maximize your score and succeed in the Endocrinology, Diabetes, and Metabolism Exam.

EBR provides you with case-based questions aligned with the ABIM blueprint and the most effective tools for building confidence as you prepare for the endocrine board exam.

https://www.endocrine.org/ebr/ebr2023

CEU 2023
CLINICAL ENDOCRINOLOGY UPDATE

Sept. 21 – 23, 2023/Virtual Only

The Endocrine Society's Clinical Endocrinology Update (CEU) provides an annual update on the latest diagnosis and treatment recommendations for various endocrine conditions, delivering educational value for clinicians, and ensuring optimal patient care worldwide.

Our program is the best way to stay updated on the latest developments in patient diagnosis and treatment in endocrinology. Esteemed faculty from across the globe will present a comprehensive, case-based agenda to help you gain knowledge to improve your practice in an intimate atmosphere where you have direct access to experts in hormone health. Our faculty will cover key endocrinology topics, including adrenal, calcium and bone, diabetes mellitus, pituitary, obesity and lipids, reproduction, and thyroid.

This year's program will be delivered online and will be accessible via our virtual meeting platform.

https://ceu2023.endocrine.org

RELAXIN 2023: 9th International Conference on Relaxin and Related Peptides

Canmore, Alberta, Canada
September 17 – 21, 2023

This conference is designed for basic, translational, and clinical scientists around the world who are interested in relaxin and related peptides, and their receptors. Featured presenters cover all aspects of basic biology and physiology, plus potential clinical applications of relaxin and related peptides. Additional topics include receptor function and signaling, reproductive and endocrine function, neurobiology, vascular and cardiac actions, matrix remodeling, drug development, and novel therapeutic targets.

https://www.relaxinconferences.com/

2023 American Thyroid Association Annual Meeting

Washington, D.C.
September 27 – October 1, 2023

The ATA Annual Meeting is the world's preeminent event for those interested in thyroid diseases and disorders and provides an opportunity for peer-to-peer learning and collaboration through lectures, interactive discussions, meet the professor sessions, and abstracts. This year, the ATA will celebrate its centennial anniversary with a culmination of the celebration and the largest gathering of thyroidologists in the world. Whether you're an endocrinologist, a surgeon, an advanced practice provider, a fellow in training, or a medical student, the topics covered during the meeting will provide in-depth information about thyroid diseases and disorders. With a diverse program planned, attendees can customize their experience by attending sessions

that are most important to their professional development.
https://www.thyroid.org/2023-annual-meeting/

ObesityWeek® 2023

Dallas, Texas
October 14 – 17, 2023

The preeminent international conference for obesity researchers and clinicians, ObesityWeek® is home to the latest developments in evidence-based obesity science: cutting-edge basic and clinical research, state-of-the-art obesity treatment and prevention, and the latest efforts in advocacy and public policy. Overcoming obesity requires multidisciplinary approaches. This is the conference that encompasses the full spectrum of obesity science from basic science research, to translational research and clinical application, to public policy; diet, exercise, lifestyle, and psychology to medical and surgical interventions; from pediatric to geriatric to underserved populations.
https://obesityweek.org/

4th Annual Mayo Clinic Thyroid and Parathyroid Disorders Course 2023

Orlando, Florida
November 9 – 11, 2023

The 4th Annual Mayo Clinic Thyroid and Parathyroid Disorders Course 2023 is a three-day CME course offering a comprehensive review of diagnostic techniques and medical and surgical management of thyroid and parathyroid disorders.
https://ce.mayo.edu/endocrinology/

Neuroscience 2023 – Society for Neuroscience (SfN)

Washington, D.C.
November 11 – 15, 2023

Each year, scientists from around the world congregate to discover new ideas, share their research, and experience the best the field has to offer. Attend so you can: Present research, network with scientists, attend session and events, and browse the exhibit hall. Join the nearly half a million neuroscientists from around the world who have propelled their careers by presenting an abstract at an SfN annual meeting — the premier global neuroscience event.
https://www.sfn.org/meetings/neuroscience-2023

INTERNATIONAL **ITINERARY**

The 61st Annual ESPE Meeting 2023

The Hague, The Netherlands
September 21 – 23, 2023

The theme for the European Society for Paediatric Endocrinology's (ESPE) 61st Meeting is "Global Challenges in Pediatric Endocrinology," which will address several important challenges from around the world: carbon dioxide-driven climate change; global but also local inequality with large differences in access to basic needs and medical care; and a recent pandemic. Climate change calls for more sustainable medical care in the field of pediatric endocrinology and also raises ethical questions. Another big challenge is the ever-rising prevalence of obesity, with low- and middle-income countries quickly catching up with high-income countries. Although considerable advances are made with respect to medical treatment, these are not automatically available for large groups of affected individuals. Both experienced colleagues and younger trainees will have the opportunity to present their work in oral sessions with ample opportunities for further presentations and discussion in the poster sessions, which will include both physical and electronic posters. The meeting will be held in World Forum, an iconic international event venue located between the beach and the city center in the "City of Peace and Justice."
https://www.eurospe.org/events-espe/espe-2023-annual-meeting/

EndoBridge 2023

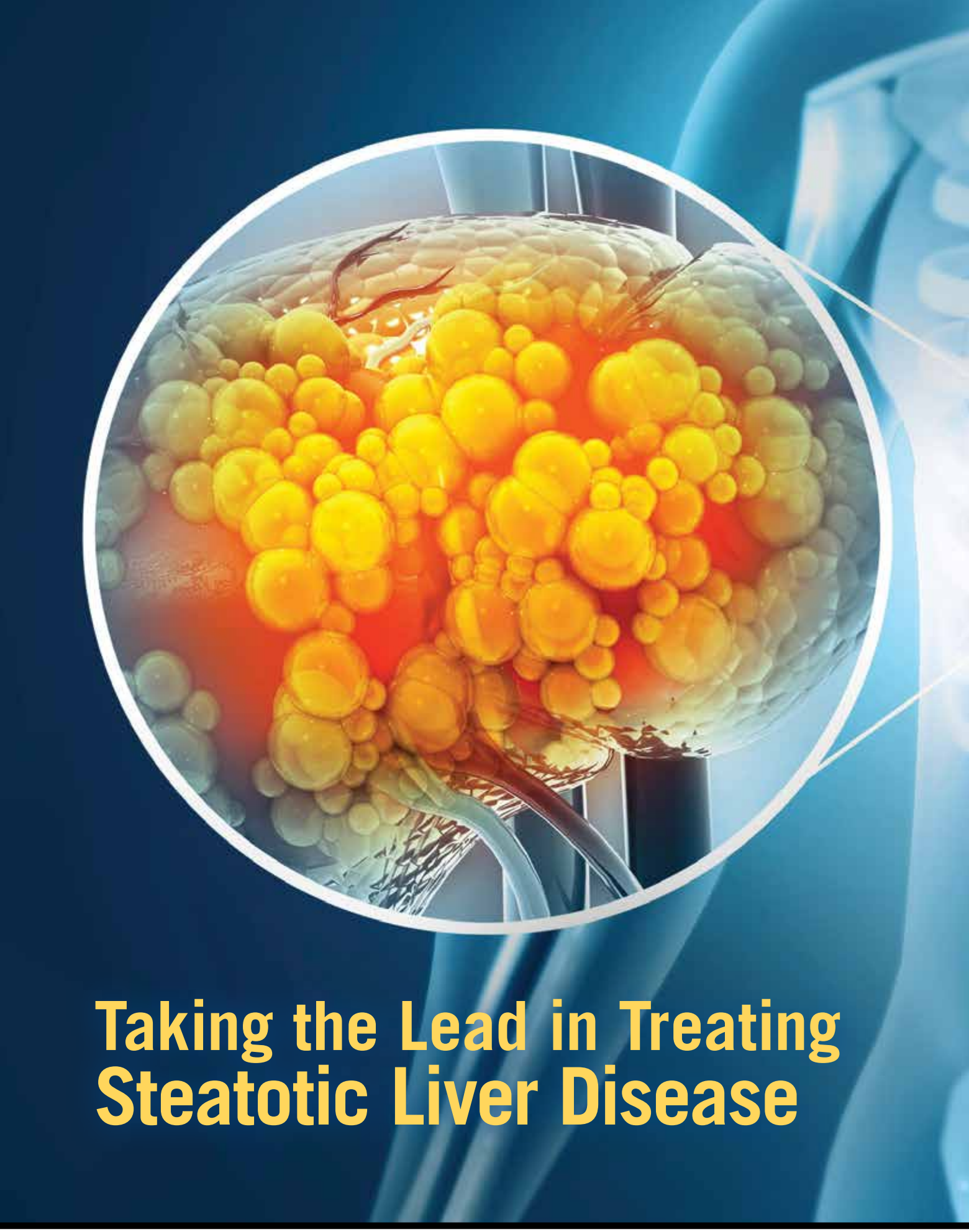
Antalya, Turkey
October 19 – 22, 2023

Co-hosted by the Endocrine Society and the European Society of Endocrinology in collaboration with the Society of Endocrinology and Metabolism of Turkey, EndoBridge will be held in English with simultaneous translation into Russian, Arabic, and Turkish. Accredited by the European Accreditation Council for Continuing Medical Education (EACCME), this three-day scientific program includes state-of-the-art lectures delivered by world-renowned faculty and interactive sessions covering all aspects of endocrinology. EndoBridge® provides a great opportunity for physicians and scientists from around the world to interact with each other, share their experience and perspectives, and participate in discussions with global leaders of endocrinology.
www.endobridge.org

Third Euro Diabetes and Endocrinology Congress

Paris, France
December 11 – 12, 2023

The Third Euro Diabetes and Endocrinology Congress is a unique forum for diabetologists and endocrinologists with comparable levels of experience and education to present, exchange ideas, and develop collaborative networks in both academia and industry.
https://diabetic.plenareno.com/

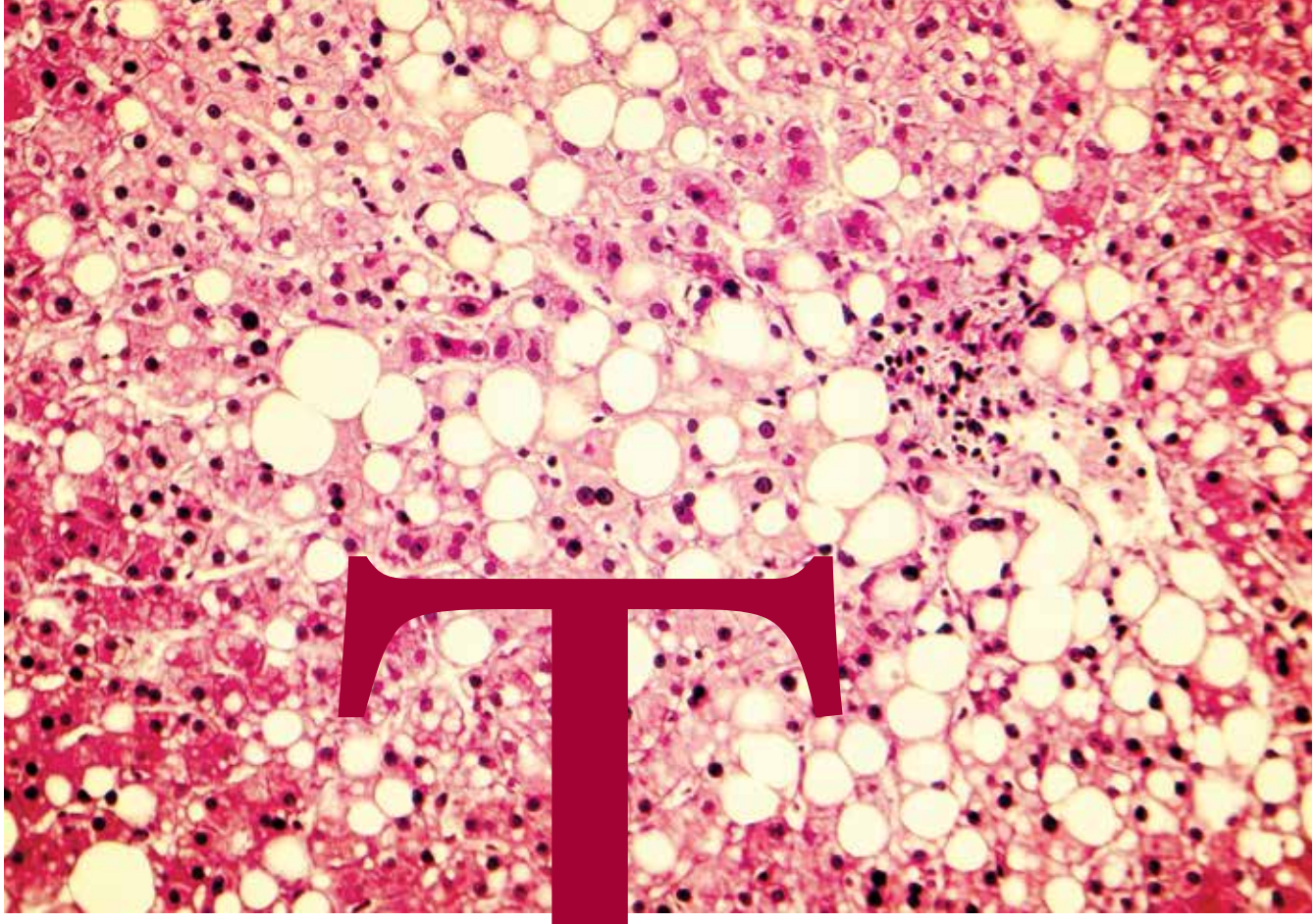


Taking the Lead in Treating Steatotic Liver Disease

Endocrine TARGETS

BY ERIC SEABORG

Endocrine dysfunction plays a prominent role in the development of steatotic liver disease and was featured prominently with a multi-session program at ENDO 2023. Endocrinologists will be on the front lines to help patients stave off this disorder that will no longer be known as "fatty liver disease," which is projected to become the leading cause of liver transplants.



Because endocrine dysfunction plays a prominent role in the development of steatotic liver disease, endocrinologists could play a larger role in its prevention and treatment, several specialists tell *Endocrine News.*

To raise awareness of endocrinologists' importance for this condition, **ENDO 2023** included a session on endocrine targets in steatotic liver disease — and as a reflection of attendees' interest, the room had to be enlarged to accommodate all those who wished to attend.

In the time since that session was organized, the American Association for the Study of Liver Diseases published in the journal *Hepatology* an international, multisociety consensus statement delineating new nomenclature for fatty liver disease that aims to be more precise and avoid stigmatizing language.

The statement says "steatotic liver disease was chosen as the overarching term to encompass the various etiologies of steatosis." The term metabolic dysfunction-associated steatotic liver disease (MASLD) will replace nonalcoholic fatty liver disease, and metabolic dysfunction-associated steatohepatitis (MASH) will replace nonalcoholic steatohepatitis. *(See the sidebar on page 25 for more details on the new nomenclature. To avoid confusion, this article will conform to the new nomenclature.)*

Endocrinologists Take the Lead

The impact of MASLD has grown so much with the increase in obesity and diabetes that MASLD is expected to become the leading cause of liver transplants.

"Endocrinologists should take a lead in treating MASLD because the increase in incidence of this disorder is in large part driven by metabolic factors," says Karen Klahr Miller, MD, the moderator of the **ENDO** session. Miller is a professor of medicine

at Harvard Medical School and chief of the neuroendocrine unit at Massachusetts General Hospital. "In treating the root causes of MASLD, endocrinologists can have a significant impact on the incidence, prevalence, and morbidity of the disorder. For similar reasons, we should also take a lead in research in this area. We can and should identify metabolic and endocrine therapeutic targets and test potential new treatments for MASLD."

"In addition to the obvious link with obesity, diabetes, and insulin resistance, many other conditions that we treat as endocrinologists impact MASLD and MASH," says Laura E. Dichtel, MD, MHS, one of the speakers at the session, who is an assistant professor at Harvard Medical School and the director of steatotic liver disease research in the Neuroendocrine Unit at Massachusetts General Hospital. "Many of the hormones that we manage as endocrinologists have been implicated in the pathophysiology of MASLD or MASH — including thyroid hormone, cortisol, sex steroid, and growth hormone. Patients with polycystic ovary syndrome and post-menopausal women have been shown to be at higher risk of MASLD and MASH. Endocrine conditions are inherently intertwined in the pathophysiology of the disease and have the potential to impact the early-stage disease development and progression."

Intrigued by the role of these hormones, Dichtel has researched growth hormone's effects. Some clues to the hormone's importance are that patients with acromegaly have very high growth hormone levels and low levels of liver fat, whereas, in contrast, patients with hypopituitarism and severe growth hormone deficiency have higher levels of liver fat. Growth hormone levels of patients with obesity can be 25% lower than those of lean individuals.

To explore the role of growth hormone, Dichtel led a team that conducted a six-month, randomized, double-blind, placebo-controlled trial among 53 adults with BMIs greater than 25 and MASLD without diabetes that was published this year in *The Journal of Clinical Endocrinology & Metabolism*. The test group received daily

Karen Klahr Miller, MD
professor of medicine, Harvard Medical School; chief, Neuroendocrine Unit, Massachusetts General Hospital, Boston, Mass.

> "In treating the root causes of MASLD, endocrinologists can have a significant impact on the incidence, prevalence, and morbidity of the disorder. For similar reasons, we should also take a lead in research in this area. We can and should identify metabolic and endocrine therapeutic targets and test potential new treatments for MASLD."

Opposite page: Fatty liver, now called liver steatosis. Photomicrograph showing large vacuoles of triglyceride fat accumulated inside liver cells, it occurs in alcohol overuse, under action of toxins, in diabetes.

This page: Testing for insulin like growth factor 1 (IGF-1) is recommended to explore the role of growth hormone in reducing liver fat, improving the liver enzyme ALT, reducing visceral adipose tissue, and reducing high-sensitivity C-reactive protein levels.

Laura E. Dichtel, MD, MHS, assistant professor, Harvard Medical School; director, steatotic liver disease research in the Neuroendocrine Unit, Massachusetts General Hospital, Boston, Mass.

> Another important aspect of MASLD is that it can often go undiagnosed. Endocrinologists have the ability to screen and identify patients at higher risk for progression who are developing inflammation fibrosis and need to be monitored by our hepatology colleagues. We are truly on the frontlines of recognizing MASLD and treating the comorbidities that can lead to its progression.

subcutaneous injections of growth hormone targeted to raise their IGF-1 levels to the upper-quartile of the normal range. The researchers assessed liver fat using proton magnetic resonance spectroscopy before and after the trial and found that the treatment group showed a significant reduction in liver fat. The mean treatment effect between the two groups was a 9% reduction in liver fat with growth hormone, and the treatment group's relative reduction was 20%. The two groups maintained their weight, so the improvement was not related to weight loss.

"We were able to show that growth hormone administration in this population improved the MASLD phenotype and associated metabolic risk factors. Growth hormone administration reduced liver fat, improved the liver enzyme ALT, reduced visceral adipose tissue, and reduced high-sensitivity C-reactive protein levels. There were no safety issues identified," Dichtel says.

Mouse Models

Another speaker at the session also related her studies of growth hormone in MASLD. Rhonda D. Kineman, PhD, professor in the Division of Endocrinology, Diabetes, and Metabolism at the University of Illinois at Chicago and research career scientist at the Jesse Brown VA Medical Center, has used mouse models that allow for adult-onset, hepatocyte-specific knockdown of the GH receptor and manipulation of its downstream targets.

"These studies show that GH acts directly on the hepatocytes of the liver to control excess fat accumulation, as well as protecting against liver injury due to excess caloric intake. Investigations are ongoing to dissect the mechanisms by which GH has these effects in hopes of unveiling novel targets to treat MASH," Kineman says.

Because GH treatment requires daily injections, frequent monitoring, and is expensive, Kineman doubts that using growth hormone to treat MASLD and MASH is a viable option at this point. "Too much growth hormone is not a good thing, and it is a hard hormone to manage in a therapeutic range without the negative consequences," she says. "But perhaps over the next few years, we will find ways to raise endogenous

Endocrinologists can take a lead role in the treatment of steatotic liver disease, primarily by engaging patients with early interventions to prevent its progression.

Endocrine dysfunction plays a prominent role in the development of steatotic liver disease, which is projected to become the leading cause of liver transplants.

New Nomenclature Avoids Stigmatizing Language

In a consensus statement in the journal *Hepatology*, the American Association for the Study of Liver Diseases (AASLD) noted that after it became clear that being overweight or obese is associated with hepatic steatosis, the term nonalcoholic fatty liver disease gained widespread use.

However, the statement notes the terminology was problematic because "it has always been appreciated that the term 'nonalcoholic' did not accurately capture what the etiology of the disease was, and the term 'fatty' has been considered to be stigmatizing by some. Language can create or exacerbate stigma, marginalize segments of the affected population, and ultimately, contribute to health inequalities."

The AASLD organized a Delphi panel of 236 participants from 56 countries with the conclusion endorsed by more than 60 organizations spanning the globe. A statement on the AASLD website summarized the key points in the new nomenclature and abbreviations as:

- Steatotic liver disease (SLD) was chosen as an overarching term to encompass the various etiologies of steatosis.
- The term steatohepatitis was retained as an important pathophysiological concept.
- The term metabolic dysfunction-associated steatotic liver disease (MASLD; pronounced: Ma-zuld) replaces nonalcoholic fatty liver disease. MASLD includes patients who have hepatic steatosis and at least one of five cardiometabolic risk factors.
- MetALD (pronounced: Met A-L-D) is a new category, separate from pure MASLD, that includes patients with MASLD who consume significant amounts of alcohol.
- Metabolic dysfunction-associated steatohepatitis (MASH) is the replacement term for nonalcoholic steatohepatitis.
- Cryptogenic SLD is the term for those with no metabolic dysfunction and no known cause of their SLD.

The AASLD believes that "with the new nomenclature, we now have an affirmative name and diagnosis without using stigmatizing language."

"There have been some debates in the past about nomenclature leading up to this," says Laura E. Dichtel, MD, MHS, of Harvard Medical School and Massachusetts General Hospital, who was not involved in developing the guidelines. "This consensus statement uniformly reframes and gives clear guidelines to categorize steatotic liver disease. The new terminology has already begun to be adopted and will hopefully support advances in research and clinical care by defining steatotic liver disease more precisely."

More information and a link to the consensus statement can be found at: **https://www.aasld.org/new-nafld-nomenclature**.

Rhonda D. Kineman, PhD, professor, Division of Endocrinology, Diabetes, and Metabolism, University of Illinois at Chicago; research career scientist, Jesse Brown VA Medical Center, Chicago, Ill.

> “Too much growth hormone is not a good thing, and it is a hard hormone to manage in a therapeutic range without the negative consequences. But perhaps over the next few years, we will find ways to raise endogenous growth hormone levels or develop drugs that directly target mechanisms downstream of GH receptor signaling to directly treat MASLD.”

A patient prepares a semaglutide injection. Already approved for use in weight loss and type 2 diabetes, this drug has also been shown to improve hepatic parameters in patients with MASH.

growth hormone levels or develop drugs that directly target mechanisms downstream of GH receptor signaling to directly treat MASLD.”

Drugs and Prevention

Such an option would be welcome because there are no Food and Drug Administration-approved drugs to treat MASLD, per se. But there are options among drugs currently in use, primarily for weight loss and diabetes treatment, according to speaker Diana Barb, MD, a clinical associate professor in the Division of Endocrinology, Diabetes, and Metabolism at the University of Florida.

For example, the GLP-1 receptor agonist semaglutide, approved for use in weight loss and type 2 diabetes, has been shown to improve hepatic parameters in patients with MASH. The thiazolinedione pioglitazone improves liver histology in patients with and without type 2 diabetes. Barb notes that currently a leading approach seems to be a combination of drugs that endocrinologists are already using to treat type 2 diabetes and obesity.

In addition, bariatric surgery, with its associated weight loss and other benefits, is effective for long-term MASH resolution and fibrosis regression. These approaches are in the armamentarium that endocrinologists are accustomed to using in related conditions.

“It is definitely in endocrinologists’ wheelhouse to address lifestyle modification, diet, exercise, hyperlipidemia, type 2 diabetes, and overweight/obesity,” says Dichtel. “Another important aspect of MASLD is that it can often go undiagnosed. Endocrinologists have the ability to screen and identify patients at higher risk for progression who are developing inflammation fibrosis and need to be monitored by our hepatology colleagues. We are truly on the frontlines of recognizing MASLD and treating the comorbidities that can lead to its progression.” EN

–SEABORG IS A FREELANCE WRITER BASED IN CHARLOTTESVILLE, VA. IN THE MAY ISSUE, HE WROTE ABOUT THE **ENDO 2023** SYMPOSIUM “ADDRESSING RACIAL AND ETHNIC DISPARITIES IN OSTEOPOROSIS CARE.”

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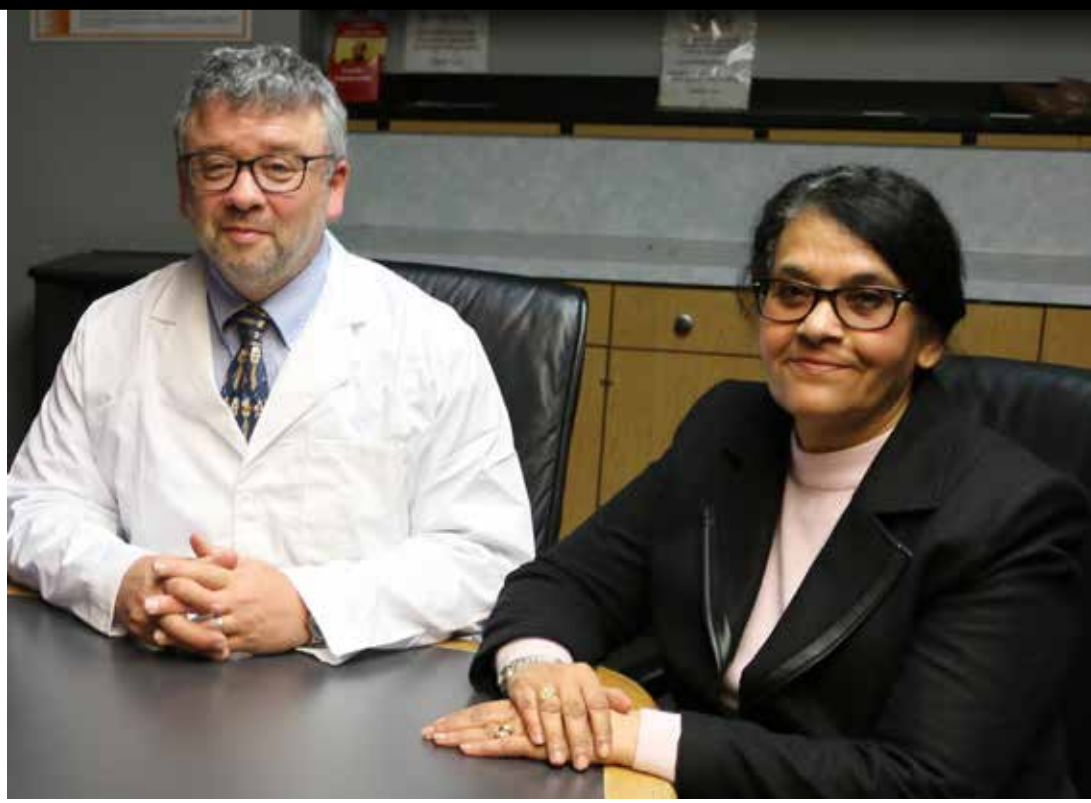
ENDOCRINE SOCIETY

GUILT BY *Association*

The concerning link among NASH, MAFLD, Diabetes, and Obesity

As obesity rates continue to climb so does metabolic-associated fatty liver disease (MAFLD), often at an alarming rate. *Endocrine News* talks to Theodore C. Friedman, MD, PhD, and Magda Shaheen, MD, PhD, MPH, MS, about research they presented at ENDO 2023 on fatty liver disease's link to diabetes, what impact new medications could have, and how endocrinologists can help stem the tide.

BY DEREK BAGLEY



Theodore C. Friedman, MD, PhD, chair, Department of Internal Medicine (left), and Magda Shaheen, MD, PhD, MPH, MS, program director, Master of Science in Clinical Research Program. Charles R. Drew University of Medicine & Science, Los Angeles, Calif.

As of now, about 42% of Americans have obesity — a condition that needs no introduction here, but certainly needs to be revisited from time to time. In seven years or so, half of Americans are projected to have obesity, which of course carries with it all kinds of comorbidities, including fatty liver disease — which has no cure but can be successfully treated by treating the underlying condition of obesity. But things have gotten tricky.

The percentage of metabolic-associated fatty liver disease (MAFLD) is increasing in U.S. adults, according to a study presented at **ENDO 2023**. And the rate of fatty liver disease is outpacing that of obesity.

MAFLD, alternatively known as non-alcoholic fatty liver disease (NAFLD), is fast becoming the most common indication for liver transplantation. It is a risk factor for cardiovascular disease and type 2 diabetes. If untreated, MAFLD can lead to liver cancer and liver failure.

"MAFLD affects Hispanics at a higher prevalence relative to Blacks and whites. This racial/ethnic disparity is a public health concern," says researcher Theodore C. Friedman, MD, PhD, chair of the Department of Internal Medicine at Charles R. Drew University of Medicine and Science and the lead physician in endocrinology at the Martin Luther King, Jr. Outpatient Center in Los Angeles, Calif. "Overall, the increase in MAFLD is concerning, as this condition can lead to liver failure and cardiovascular diseases and has an important health disparity."

The researchers analyzed data for 32,726 participants from the National Health and Nutrition Examination Survey (NHANES) from 1988 to 2018. "We found that overall, both MAFLD and obesity increased with time, with the increase in MAFLD greater than the increase in obesity," Friedman says.

"The percent of people with MAFLD increased from 16% in 1988 to 37% in 2018 (a 131% increase) while the percent of obesity rose from 23% in 1988 to 40% in 2018 (a 74% increase)," the study's first author Magda Shaheen, MD, PhD, MPH, MS, program director, Master of Science in Clinical Research Program, Charles R. Drew University of Medicine and Science, said in a statement. "The prevalence of MAFLD increased faster than the prevalence of obesity, suggesting that the increase in the other risk factors such as diabetes and hypertension may also contribute to the increase in the prevalence of MAFLD."

Among Mexican Americans, the percentage of MAFLD was higher at all times compared to the overall population. The percent increase of MAFLD in 2018 relative to 1988 was 133% among whites, 61% among Mexican Americans, and 56% among Blacks.

These findings coincide with those reached by Friedman and his co-authors of a paper recently published in *Frontiers of Endocrinology*, in which the authors conclude, "that prediabetes and diabetes populations had a high prevalence and higher odds of NAFLD relative to the normoglycemic population, and HbA1c is an independent predictor of NAFLD severity in prediabetes and diabetes populations."

Endocrine News caught up with Friedman and Shaheen to talk about this alarming increase in fatty liver disease, diabetes's relationship with fatty liver disease, and what can be done to curb this trend.

Your ENDO study shed light on some pretty troublesome findings. What are the implications for this increase in the prevalence of fatty liver disease?

Theodore C. Friedman: Some patients with fatty liver will go on to nonalcoholic steatohepatitis (NASH) and cirrhosis and require a liver transplant. It's also associated with increased cardiovascular disease. It's a common disease getting more common. As we pointed out, it's growing more than just obesity is. I think it's a bad diet, unhealthy things, more diabetes, more fatty liver disease, more obesity. I think endocrinologists need to be at the forefront of pushing healthy lifestyle and getting our patients, no matter what they say, to try to be better, exercise more, and be healthier.

Can you talk a little bit about the difference between NAFLD to MAFLD?

Magda Shaheen: MAFLD is defined as fatty liver disease (FLD) with overweight/obesity, evidence of metabolic dysregulation, or type 2 diabetes mellitus. Non-alcoholic fatty liver disease (NAFLD) is defined as FLD without excessive alcohol consumption or other causes of chronic liver disease.

TCF: We and other endocrinologists prefer the term MAFLD because 1) that reflects that it's an endocrine disease and needs to be on endocrinologists' radar; 2) it reflects the metabolic nature of the condition; and 3) it's not defined by

"MAFLD is defined as fatty liver disease (FLD) with overweight/obesity, evidence of metabolic dysregulation, or type 2 diabetes mellitus. **Non-alcoholic fatty liver disease (NAFLD) is defined as FLD without excessive alcohol consumption or other causes of chronic liver disease."**

— MAGDA SHAHEEN, MD, PHD, MPH, MS, PROGRAM DIRECTOR, MASTER OF SCIENCE IN CLINICAL RESEARCH PROGRAM, CHARLES R. DREW UNIVERSITY OF MEDICINE & SCIENCE, LOS ANGELES, CALIF.

the absence of alcohol. Some people with fatty liver disease may consume alcohol.

We spoke before about the disparities of fatty liver disease affecting Hispanics more than Black or white people, and that it affects Mexican Americans even more so among Hispanics.

TCF: Correct, the rate of [liver disease in] Hispanics that are not Mexican Americans is similar to other races. Mexican Americans should especially be screened for MAFLD and have ethnically appropriate interventions.

The fact that liver disease seems to be outpacing obesity is, again, troubling. What does this mean for patients and the physicians treating them? And in your opinion, what can be done to curb this trend?

TCF: More awareness and testing and emphasis on better diet and more exercise. I deal with mostly low-income, mostly Hispanic patients, and I've been at Martin Luther King since 2000. In the beginning, there was very little awareness of diet and exercise. I had some patients who weighed 300 pounds; they came in with cellulitis and infections. And they said, "Nobody ever talked to me about losing weight." Now, everybody knows about adopting a healthy lifestyle. People, regardless of where they live and their education, they've heard it before. They may not know some specifics. They may not know some hints. They may not know exactly what to eat. I think there's a lot of missing information about what kind of food to eat.

I think the art of this is how to motivate people, how to figure out what their barriers are, and how to inspire them to change. We do an obesity group visit at MLK, and we talk about these things. We're actually starting a lifestyle medicine group visit with our family medicine and internal medicine residents, which is a big effort. I think a group setting is probably better than an individual setting; you get more inspiration from the audience, and people buy into it. We talk a little bit about fatty liver disease and why it's important to prevent it. I think this is what endocrinologists need to be doing these days, in addition to giving people insulin, for example; they need to spend a good portion of their visit really trying to get them motivated to improve their lifestyle.

Is there any interest in Ozempic or these new weight loss, anti-obesity medications?

TCF: Ozempic does help with fatty liver disease. Mounjaro does also. For patients who are appropriate to go on them, I use them, mostly for people already with diabetes who are at the stage of their diabetes that they would either go onto

insulin or to go onto one of these medicines. I would have them go on Ozempic/Mounjaro.

I think it brings up two points. One is, people often eat unhealthy foods, and if they can have decreased cravings for these unhealthy foods — which Ozempic does — it takes away some of your cravings for junk foods. You're not as hungry, so when you drive by that Jack in the Box, you're not going to pull over just because you're not that hungry. It gets people to stop eating as much and have more money, just because they're not spending it all on food. They have more time. They feel better for the most part, and they see good results.

On the other hand, I think the mainstay treatment for obesity, diabetes, and MAFLD should be lifestyle changes and diet and exercise that people should be doing without having to take a medicine that often costs $1,000 a month, lead to some fair amount of side effects, and potentially bankrupt healthcare systems.

Now to the *Frontiers* paper. It seemed to dovetail with the presentation at ENDO and answer some questions as to why fatty liver disease is outpacing obesity.

TCF: Definitely. They're both related.

Can you speak more to the "bidirectional relationship" of diabetes and liver disease?

TCF: Diabetes clearly leads to more liver disease — the higher the A1c, the more fatty liver disease. We did correlations, so we can't say for sure if more severe liver disease leads to more diabetes. I think it's clear diabetes and pre-diabetes lead to fatty liver disease, but there is a paper that supports fatty liver disease leading to diabetes.

[Shaheen points to a 2021 paper by Khneizer, et al., who write, "There is a close bi-directional relationship between NAFLD and type 2 diabetes mellitus (T2DM); NAFLD increases the risk for T2DM and its complications whereas T2DM increases the severity of NAFLD and its complications."]

You write about the need for glycemic control to reduce the odds of severe NAFLD.

MS: Our study showed that among those with prediabetes and diabetes, increased A1c was associated with an increased chance of NAFLD.

> Diabetes clearly leads to more liver disease — the higher the A1c, the more fatty liver disease. We did correlations, so we can't say for sure if more severe liver disease leads to more diabetes. **I think it's clear diabetes and pre-diabetes lead to fatty liver disease, but there is a paper that supports fatty liver disease leading to diabetes."**
>
> — THEODORE C. FRIEDMAN, MD, PHD, CHAIR, DEPARTMENT OF INTERNAL MEDICINE, CHARLES R. DREW UNIVERSITY OF MEDICINE & SCIENCE, LOS ANGELES, CALIF.

TCF: Studies have shown that any anti-hyperglycemic agent improves NAFLD, including both those know to improve liver disease like pioglitazone and GLP-1 receptor agonists, but also other diabetes drugs like sulfonylureas.

MS: Three antidiabetic drugs (TZD, DPP-4Is, and GLP-1RAs) are effective in reduction of liver enzymes. SGLT2Is and GLP-1RAs were superior to other diabetes medications in reducing liver fat fraction. Recent studies have reported that metformin can improve insulin resistance and hyperinsulinemia and may aid in the treatment of NAFLD. Evidence from animal and human studies has indicated that metformin may reduce the onset and progression of NAFLD.

You write, "The current study confirms that NAFLD needs to be included in the list of conditions that subjects with prediabetes may develop." Is there still a gap in that area?

TCF: Yes, many people think prediabetes is a benign condition that isn't associated with other diseases.

NAFLD itself has a racial disparity.

MS: Yes, racial/ethnic disparity existed where Mexican Americans have a higher prevalence of NAFLD and Blacks have lower prevalence of NAFLD.

Were you surprised to find no racial/ethnic disparity among those with prediabetes and diabetes?

TCF: A bit, but since Mexican Americans have both more liver disease and prediabetes/diabetes, when adjusted for race/ethnicity there was no effect.

MS: When we adjust for demographics, there was a racial/ethnic disparity in those with prediabetes. However, after adjusting for behavioral variables, the difference between Mexican Americans and whites was not observed, suggesting that one or more of the behavioral variables can account for the racial/ethnic difference.

What's the main thing you hope readers will take away from both of these studies and this article?

MS: For those with prediabetes and diabetes, glycemic control is important to reduce the chance of NAFLD and prevent the progression of the disease.

TCF: MAFLD is a serious and increasing condition related to metabolic dysfunction, prediabetes, and diabetes, and is increasing with time. A better lifestyle is needed to stem the tide. EN

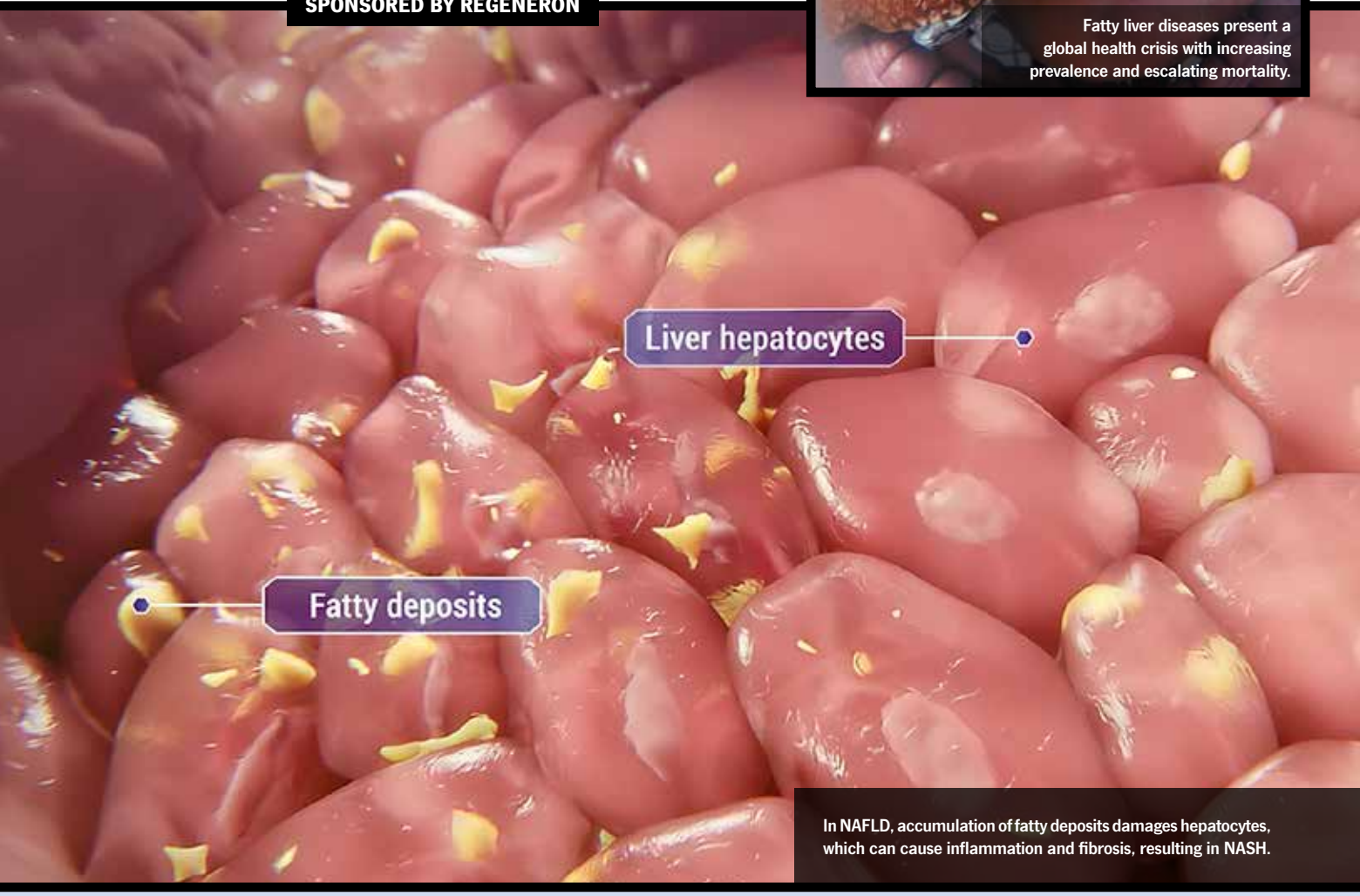
– BAGLEY IS THE SENIOR EDITOR OF *ENDOCRINE NEWS*. IN THE AUGUST ISSUE, HE WROTE ABOUT SOME OF THE BREAKING SCIENTIFIC NEWS THAT WAS PRESENTED AT **ENDO 2023**.

Non-Alcoholic FATTY LIVER DISEASE:

The Silent Epidemic and Emerging Research for Detection and Treatment

BY ABHINAV SETH, MD, PHD, AND ROBERTO CALLE, MD

Fatty liver diseases present a global health crisis with increasing prevalence and escalating mortality.



In NAFLD, accumulation of fatty deposits damages hepatocytes, which can cause inflammation and fibrosis, resulting in NASH.

Along with the public health challenges of obesity and diabetes, endocrinologists are now becoming keenly aware of the prevalence of another ominous threat: non-alcoholic steatohepatitis (NASH). Endocrine Society members Abhinav Seth, MD, PhD, and Roberto Calle, MD, both with Regeneron, give *Endocrine News* an exclusive primer on this disorder, as well as a future path for diagnosis, assessment, and treatment.

Non-alcoholic fatty liver disease (NAFLD)* is a condition associated with accumulation of fat in the liver in the absence of excess alcohol consumption. NAFLD can progress to liver inflammation and hepatocyte injury (non-alcoholic steatohepatitis, NASH), which in some patients causes slow, progressive, and severe damage to the liver in the form of fibrosis, and ultimately cirrhosis. It may also lead to hepatocellular cancer and liver transplant and is associated with an increased cardiovascular risk.[1]

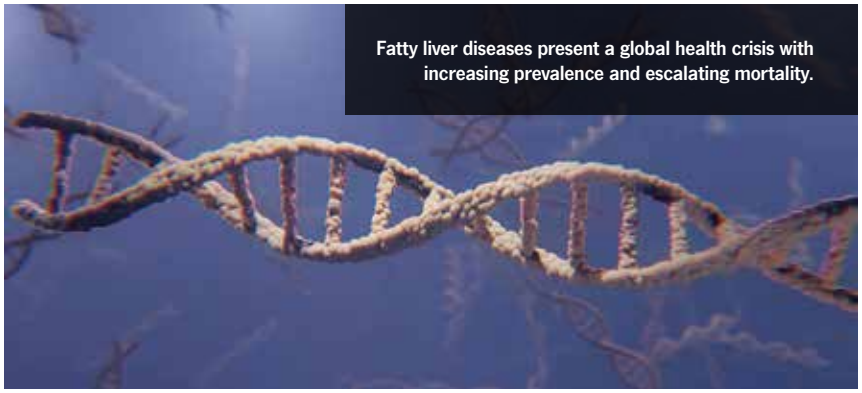
The pathophysiology of NASH is complex and is associated with metabolic changes that result in increased deposition and generation of fat in the liver. Lipotoxic damage to hepatocytes typically ensues with resulting inflammation and enhanced fibrogenic drive.[2] Risk factors for NASH include obesity, type 2 diabetes, insulin resistance, and dyslipidemia.[3]

There are numerous challenges to addressing NASH. Prevalence is rising alongside its risk factors and is likely to soon become the primary reason for liver transplants worldwide. Between 2015 and 2030, the prevalence of NASH is expected to increase by 63%.[4] Yet there are no approved treatments to slow or prevent progression of the disease. Furthermore, NASH diagnosis is only by liver biopsy, which is invasive, painful, and expensive. Hence, there is a pressing need to identify therapeutic targets and develop corresponding treatments that address the pathology of NASH and reduce disease burden, while also advancing non-invasive methodologies for NASH diagnosis.[1]

At Regeneron, our scientists are working to address this unmet need through three key areas: genetics to drive precision medicine, a strategic pipeline of investigational NASH assets with potential for disease modification across the spectrum of the disease, and research to advance the field of non-invasive biomarkers and digital pathology for improved diagnosis and prognosis.

***Note:** In June 2023, several multinational liver societies announced new nomenclature, renaming nonalcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated steatotic liver disease (MASLD) and nonalcoholic steatohepatitis (NASH) to metabolic dysfunction-associated steatohepatitis (MASH). At Regeneron, we recognize these efforts and are working with the patient and professional liver disease communities to incorporate them appropriately.

Abhinav Seth, MD, PhD



Fatty liver diseases present a global health crisis with increasing prevalence and escalating mortality.

Addressing NASH with a Genetics-Driven Approach

By Abhinav Seth, MD, PhD

As part of the Early Clinical Development and Experimental Sciences team at Regeneron, my focus is primarily on determining whether protective human genetics associations emerging from DNA sequencing data can be pharmacologically recapitulated in human patients using siRNA therapeutics.

Therapeutic approaches for NASH have made little headway in the past decade despite ongoing research with many promising investigational candidates. The Regeneron Genetics Center® (RGC) is leading one of the largest human genetic sequencing programs in the world. This program is helping find new potential therapeutic targets for NASH by identifying genetic mutations that protect individuals who carry them against the development of NASH and cirrhosis.

We have sequenced over 500,000 human exomes and assessed phenotypic associations using de-identified health records to identify and validate three genes specifically associated with NASH and NAFLD risk: *CIDEB (Cell Death Inducing DFFA Like Effector B), HSD17B13 (Hydroxysteroid 17-Beta Dehydrogenase 13), and PNPLA3 (Patatin-Like Phospholipase Domain-Containing Protein 3)*. We believe that silencing these genes in high-risk NASH patients can serve as the basis for developing precision medicines to treat NASH.

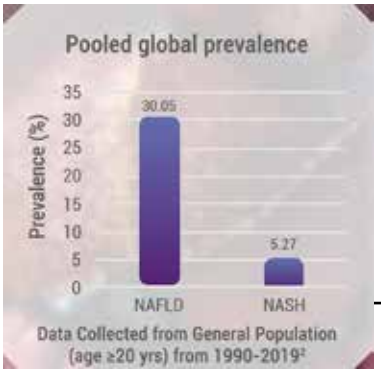
Our genetic analyses showed that a single copy of a loss-of-function mutation in the *CIDEB* gene is associated with a 53% lower risk of developing NAFLD and a 54% lower risk of developing cirrhosis.[5] *CIDEB* encodes a structural protein found in hepatic lipid droplets involved in liver fat buildup.[6]

> “By refining and optimizing the analytics processes for detecting human genes of interest in NASH and NAFLD pathophysiology, we have identified potential novel targets for a disease currently without any approved pharmacologic therapies.”

Similarly, loss-of-function in a single copy of *HSD17B13* is associated with a 17% decreased risk of non-alcoholic liver disease, while loss-of-function in both copies reduced risk by 30%.[7] *HSD17B13* also encodes for a protein found in liver cells.[8]

A missense mutation of *PNPLA3* has been previously identified as a gene of interest in liver disease by GWAS and was validated by our analyses.[9] This mutation is associated with increased hepatic triglyceride levels and an increased risk of NASH. Interestingly, we found that the protective effects of the loss-of-function variants in *HSD17B13* extend to individuals with the *PNPLA3* mutation.

These three genes may have therapeutic potential for reducing progression of NASH in patients who may be at high risk for early onset and rapid progression of the disease, illustrating the insights of genetics-based research. By refining and optimizing the analytics processes for detecting human genes of interest in NASH and NAFLD pathophysiology, we have identified potential novel targets for a disease currently without any approved pharmacologic therapies.



Above: There is a need for research on NASH treatment options beyond liver transplantation. To that end, the Regeneron Genetics Center® has sequenced the exomes of over 2 million participants, to accelerate the discover of targets and therapeutics for a variety of diseases, including NASH.

By analyzing the exome sequences and longitudinal electronic health records of more than 45,000 consented participants, Regeneron discovered a variant in the HSD17B13 gene associated with a lower risk of chronic liver disease. Encouraged by this discovery, Regeneron is further committed to understanding liver disease genetics and developing potential therapeutics to treat patients.

Left: The global presence of NAFLD has reached approximately 30% of the general population affected. The global prevalence of NASH is over 5%.

Roberto Calle, MD

> “Through meaningful engagements with patient and professional communities, we are determined to increase disease awareness and education on potential treatments for NASH at an early stage to mitigate the risks early and ultimately prevent the need for liver transplants.”

Building A Portfolio for Genetically Based Targets

By Roberto Calle, MD

In my role within the General Medicine Clinical Sciences group at Regeneron, I work closely with Abhi’s team to translate the insights they uncover in Early Development to design and conduct pivotal trials for our investigational therapies.

Because genetic changes in all three of the genes mentioned previously appear to modulate NASH risk, we are investigating siRNA assets that can silence the corresponding risk alleles specifically in the liver to determine whether we can recapitulate these effects in a clinically meaningful way. The insights from our genetic analyses have suggested potential investigational therapeutic targets of interest, but what remains is demonstrating in the clinic that silencing these targets will confer the therapeutic effects suggested by the human genetics data.

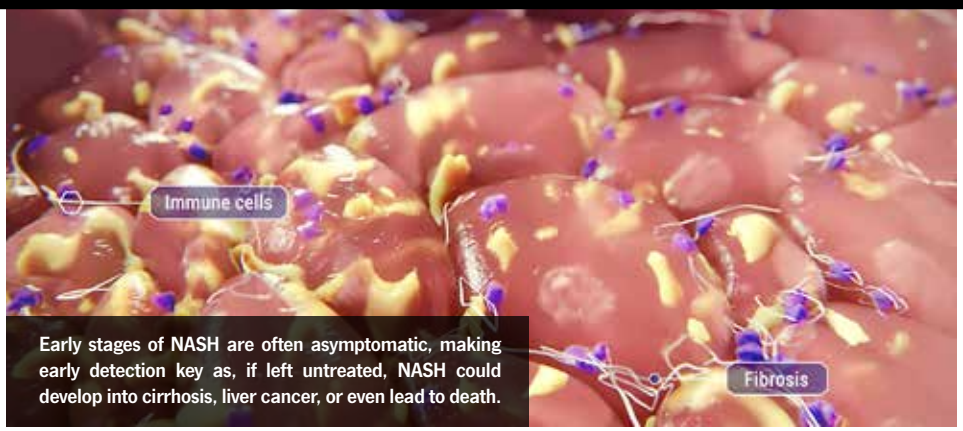
One important strategy to maintain patient safety is to make sure that the therapy is very specific in targeting the proposed mechanism. For this reason, we believe the best strategy for intercepting NAFLD and NASH etiology is using hepatocyte-targeted RNA interference (RNAi). RNAi involves the administration of short-interfering RNAs (siRNAs) that bind to the target messenger RNAs to prevent them from being translated into proteins. Conjugation to a hepatocyte-targeting ligand ensures that the siRNA is delivered specifically to the liver for silencing of the target gene with cellular resolution.

Each of our three RNAi therapeutics in clinical or preclinical development in collaboration with Alnylam, including one in Phase 2 clinical trials, is being studied to investigate diverse aspects of the pathophysiology of NASH and assess a potential precision medicine approach that addresses the specific genetic liability of each patient’s disease process.[8]

Improving Clinical Care and Research Through Biomarker Development

Looking toward the future of healthcare, we are focusing on ways to make screening, diagnosing, and monitoring patients less invasive and more scalable than traditional liver biopsies. That’s why we are partnering with academic investigators and other like-minded pharmaceutical and diagnostic companies in a public-private partnership, through the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium, to study and qualify Non-Invasive Biomarkers of Metabolic Liver Disease in a project called “NIMBLE.”[10]

The effort has already made great progress, demonstrating that several potential biomarkers may have diagnostic performance that exceeds that of commonly used blood-based markers. Such common biomarkers include the liver enzyme alanine



Early stages of NASH are often asymptomatic, making early detection key as, if left untreated, NASH could develop into cirrhosis, liver cancer, or even lead to death.

For more information about our NASH research, please visit Regeneron.com

aminotransferase (ALT) and the Fibrosis-4 (FIB-4) index, a non-invasive scoring system based on selected laboratory tests.[11] The next stages of the NIMBLE project will assess whether these potential biomarkers may be used separately or in combination as future non-invasive markers of NASH diagnosis.

AI-Enhanced Methods for Assessing Pathology

While liver biopsy remains the current reference standard for diagnosis and evaluation of NASH, we recognize that improvements in the assessment of liver pathology specimens are necessary to increase the accuracy of diagnosis and probability of detecting a treatment effect. We are therefore leveraging advances in digital pathology in our clinical trials, including machine learning and artificial intelligence, and taking bold steps by including these technologies in our clinical trial endpoints.

The state-of-the-art technologies associated with digital pathology hold tremendous potential for reducing the variability and subjectivity inherent in manual pathology reads, while substantially reducing the amount of time it takes to obtain results. Ultimately, our hope is that these scientific advancements will further streamline our processes for developing treatment options and diagnostic methods for NASH to improve disease outcomes.[12]

Pioneering the Path to Success in Diagnosis, Assessment, and Treatment

NAFLD is a rapidly emerging global manifestation of metabolic disease, and NASH is likely to become the driving force for liver transplantation worldwide. At Regeneron, we are actively pursuing this disease at multiple levels, from diagnosis to treatment, through technologically advanced methods to develop novel and less invasive assessments, and genetically informed development of precision treatments.

Through meaningful engagements with patient and professional communities, we are determined to increase disease awareness and education on potential treatments for NASH at an early stage to mitigate the risks early and ultimately prevent the need for liver transplants. Our expertise and partnerships are advancing knowledge and raising awareness for patients every day and we look forward to working with organizations like the Endocrine Society to address the challenges in NASH. EN

– SETH IS AN ASSOCIATE DIRECTOR IN THE EARLY CLINICAL DEVELOPMENT AND EXPERIMENTAL SCIENCES TEAM AT REGENERON. CALLE IS AN EXECUTIVE MEDICAL DIRECTOR IN THE GENERAL MEDICINE CLINICAL SCIENCES TEAM AT REGENERON.

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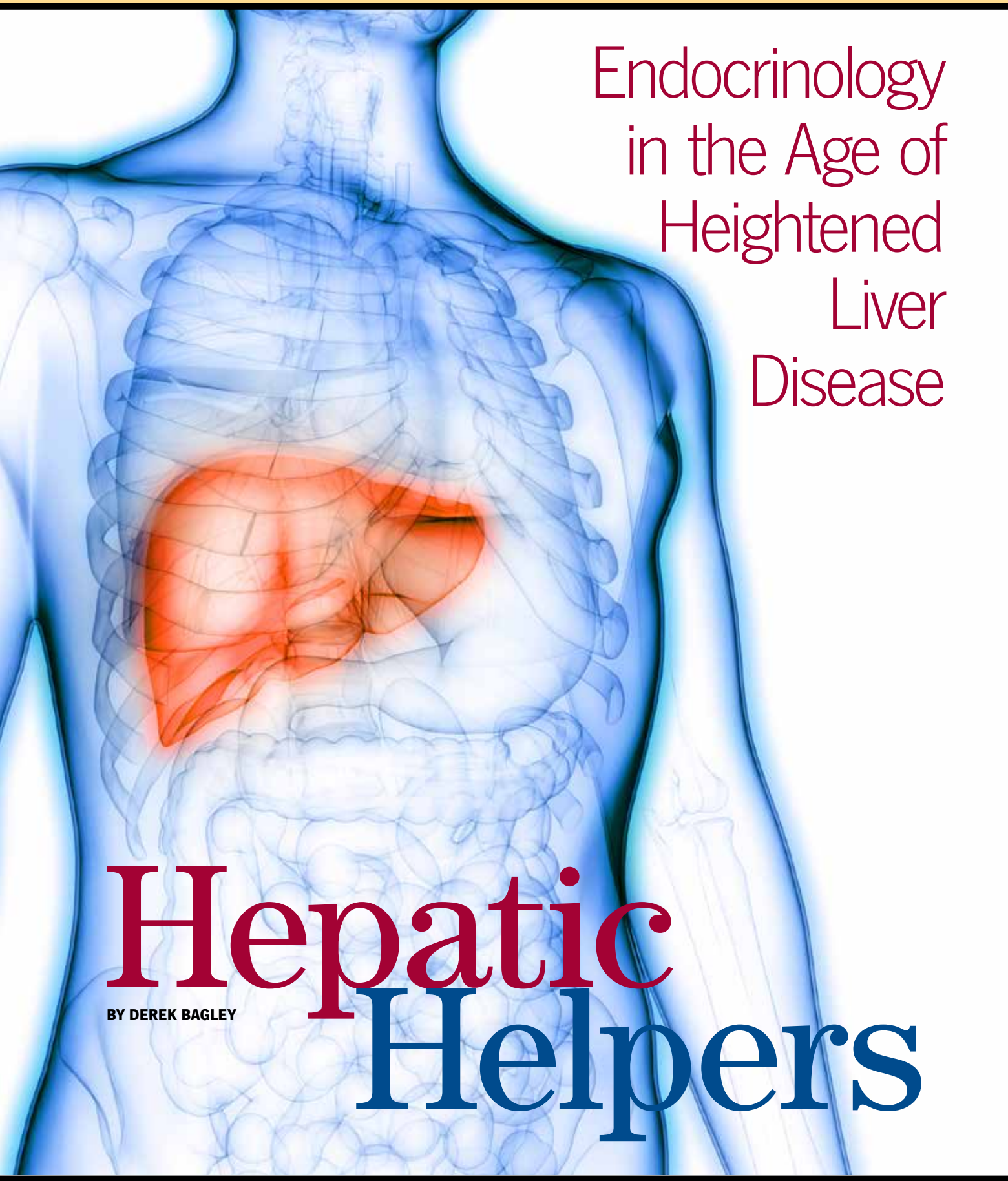


Endocrinology in the Age of Heightened Liver Disease

Hepatic Helpers

BY DEREK BAGLEY

Research published in *The Journal of Clinical Endocrinology & Metabolism* further shows the unique opportunity endocrinologists have to manage nonalcoholic liver disease and its various comorbidities. Without approved pharmaceutical solutions, endocrinologists will have much to offer in treating these ever-increasing conditions.

In an October 2022 paper published in *The Journal of Clinical Endocrinology & Metabolism*, Kenneth Cusi, MD, chief of the Division of Endocrinology, Diabetes, and Metabolism at the University of Florida in Gainesville, and his co-authors write that endocrinologists are in a unique position to prevent cirrhosis in patients with fatty liver disease, since endocrinologists already follow patients with higher risk factors for liver disease's progression — pre-diabetes, type 2 diabetes, and obesity.

The paper, "Approach to the Patient With Nonalcoholic Fatty Liver Disease," details three clinical cases of patients with nonalcoholic fatty liver disease (NAFLD) and offers an approach for the appropriate management of these patients, including treatment recommendations, from lifestyle modification to pharmacological intervention to bariatric surgery.

The paper appeared in JCEM a couple of months after a commentary Cusi wrote for the journal, in which he describes a test for identifying nonalcoholic steatohepatitis (NASH) and cirrhosis in patients with obesity or diabetes and calls for more patient and clinician awareness. "The central message for the endocrinologist is that this study confirms that the time for screening is now," Cusi writes.

"We have data that's unpublished, that shows that people who attend endocrine clinics have twice the rate of advanced liver fibrosis and cirrhosis than in primary care," Cusi says. "Because of that, we have a greater responsibility of identifying them, so they can be co-managed with hepatology and given a formal diagnosis, and some interventions that can be implemented today."

The First Step in the Right Direction

Let's start with the test. In his editorial, Cusi points to a study by Qadri, et al., that compared different tests and found that the simple panel FIB-4 covers most of what's needed as a starting point to identify patients at risk. Cusi notes that the test isn't perfect — it won't catch everyone with liver disease; this test is more designed for people with stage F3 and F4,

pre-cirrhosis and cirrhosis. Cusi says that many in the general population have F2, so the test would miss those patients. "We want to get people with advanced fibrosis F3s, so they don't develop cirrhosis," he says.

Cusi goes on to say that this test is already in electronic medical records and can almost be calculated automatically, so it would behoove an endocrinologist already treating a patient with pre-diabetes or diabetes to calculate that patient's FIB-4. "I am sure there'll be a better test developed in the future," he says. "But at least it's a first step in the right direction at no cost. The liver doctor will use imaging, will use other commercial tests, to sort out the urgency of care. But remember that, if you do this first step, I guarantee that you'll find a couple of patients with cirrhosis in your next 10 patients, and that you'll have had a unique impact in the life of some people with diabetes or obesity."

"Whether there is a causal relationship between liver fibrosis and cardiovascular mortality remains unclear. It may be that both are just the consequence of increased insulin resistance and metabolic dysfunction. But if they are indeed related, how do we go from liver fibrosis to cardiovascular mortality? **With this question in mind, we thought that as the liver produces many of the proteins in lipoproteins, changes in HDL-bound proteins could be a mechanism that puts those two together."**

– FERNANDO BRIL, MD, ASSISTANT PROFESSOR, DIVISION OF ENDOCRINOLOGY, UNIVERSITY OF ALABAMA AT BIRMINGHAM, BIRMINGHAM, ALABAMA

Rates of liver disease are passing rates of obesity, so endocrinologists will have more and more chances to have that impact on a patient's life. Cusi says most might be surprised to hear that about half of overweight people with diabetes have NAFLD, and that maybe 5% or 10% already have advanced fibrosis. Indeed, more and more experts are implicating diabetes in this spike in liver disease cases. "I like to say [diabetes and liver disease are] like a couple that get the worst out of each other," Cusi says. "They hate each other. Diabetes is affecting your liver more. And the liver is angrier and more inflamed and makes your diabetes more difficult to control. They feed off each other in the most negative way, unfortunately."

And of course, that "couple's" fights tend to spill out into other neighborhoods, namely the cardiovascular system. Now we're closer to finding the route they take to get there.

Linking Fibrosis and Cardiovascular Mortality

In January, Fernando Bril, MD, an assistant professor in the Division of Endocrinology at University of Alabama at Birmingham, and his co-authors published a paper in JCEM titled, "Differences in HDL-Bound Apolipoproteins in Patients With Advanced Liver Fibrosis Due to Nonalcoholic Fatty Liver Disease," describing how the researchers assessed

HDL-bound proteins in patients with NAFLD with or without advanced fibrosis.

The authors point out that while liver disease is associated with cardiovascular disease, the reason for that association remains unclear. Bril and Cusi studied mainly LDL particles and published a paper in 2016, showing that there were changes in patients with a fatty liver, but these were independent of histology; it was mainly the insulin resistance and the fat accumulation that were driving the changes in the LDL size.

"With that in mind, and because the liver is the one synthesizing many of the proteins in the HDL particle, we thought, 'Well, if we are looking at proteins in the HDL, we should be looking at whenever the liver synthetic function is already impaired, so that's advanced fibrosis and cirrhosis,'" Bril says. "The recent paper was looking at that: what happens with proteins bound to HDL in patients with or without advanced fibrosis due to NAFLD."

"Whether there is a causal relationship between liver fibrosis and cardiovascular mortality remains unclear," Bril continues. "It may be that both are just the consequence of increased insulin resistance and metabolic dysfunction. But if they are indeed related, how do we go from liver fibrosis to cardiovascular mortality? With this question in mind, we thought that as the liver produces many of the proteins in lipoproteins, changes in HDL-bound proteins could be a mechanism that puts those two together."

For this study, the researchers analyzed data from 185 patients who underwent liver proton magnetic resonance spectroscopy to measure intrahepatic triglyceride accumulation. Those with NAFLD underwent a percutaneous liver biopsy. They found that in cases of advanced fibrosis, there may be differences in the composition of proteins in the HDL, and they hypothesized this may play a role in HDL function.

"We have data that's unpublished, that shows that people who attend endocrine clinics have twice the rate of advanced liver fibrosis and cirrhosis than in primary care. **Because of that, we have a greater responsibility of identifying them, so they can be co-managed with hepatology and given a formal diagnosis, and some interventions that can be implemented today."**

– KENNETH CUSI, MD, CHIEF, DIVISION OF ENDOCRINOLOGY, DIABETES, AND METABOLISM AT THE UNIVERSITY OF FLORIDA, GAINESVILLE, FLORIDA

"When we order a lipid panel, we are measuring HDL cholesterol levels, but we don't really know exactly how those particles are working," Bril says. "If the protein composition of the molecules is different, this can affect the function of the HDL particle without affecting the cholesterol levels. We didn't measure cholesterol efflux in our study (a measure of HDL function), but one could hypothesize that because proteins were found to be different, maybe HDL function was also affected."

Bril is careful to say that this was only an exploratory study and is nowhere close to being used in a clinical setting. Fatty liver carries an increased risk of cardiovascular mortality, but the exact reason remains elusive. "It may be just the background of metabolic dysfunction that these patients have," Bril says. "Regardless of causality, that association exists, so healthcare providers need to pay close attention to it, and we need to be aggressive at treating dyslipidemia and all other cardio-metabolic risk factors in these patients. I think that those are

AT A GLANCE

- Liver disease cases are on the rise, and endocrinologists are in a unique position to help these patients.
- Liver disease is associated with cardiovascular disease, but that connection remains unclear. However, new research may have elucidated a pathway.
- There are no current FDA-approved treatments for liver disease. Still, endocrinologists can offer their patients treatment, starting with a simple test, as well as several weight loss interventions.

the most important messages, because results from our study are far from being applicable in the clinic."

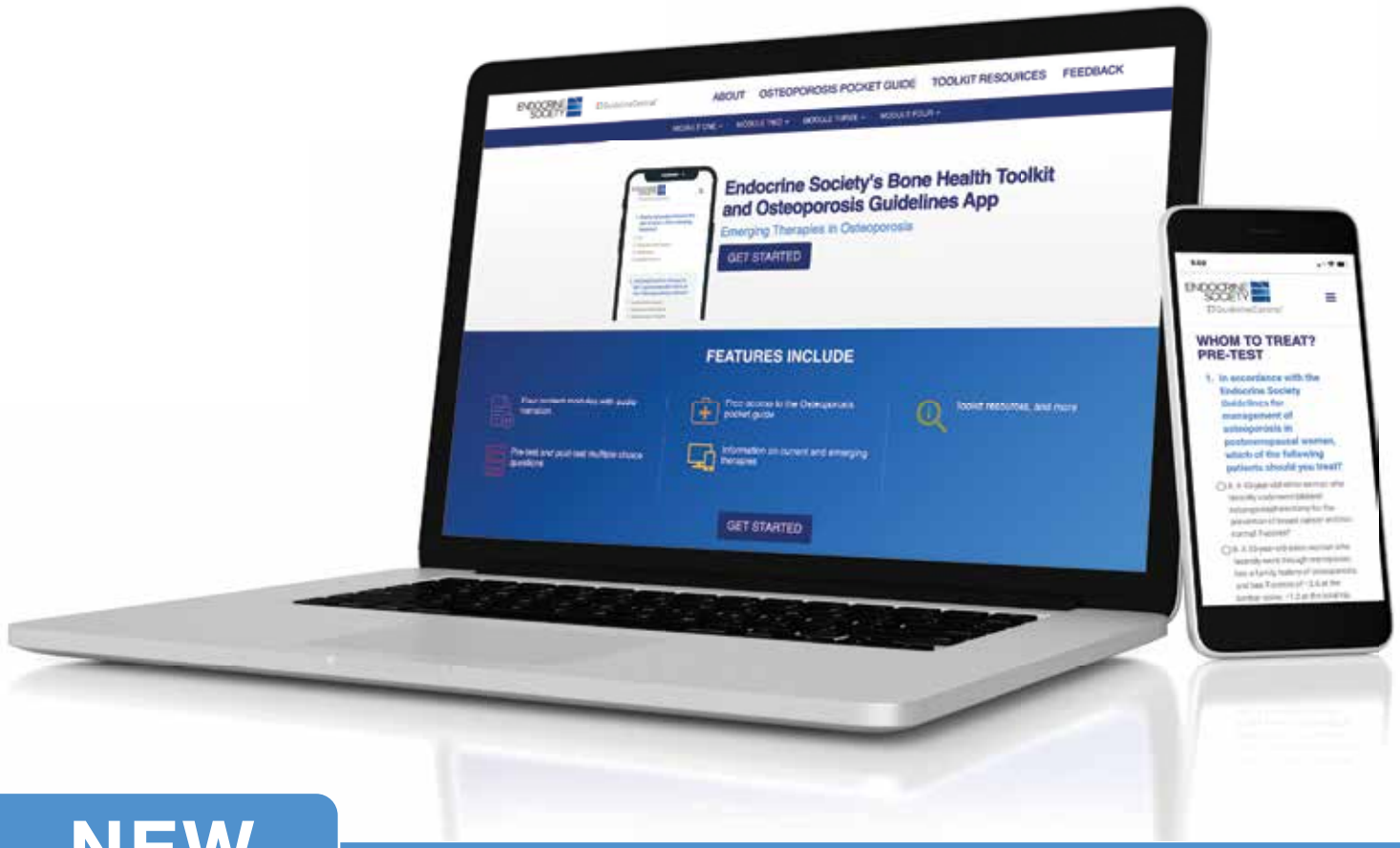
Beyond Stereotypes

As rates of fatty liver rise, so does the number of treatment options. For Cusi, the name of the game is weight loss by any means, in addition to pharmacological therapy with drugs like thiazolidine and GLP-1s. The GLP-1 receptor agonist semaglutide has been in the news lately as celebrities use it to shed pounds, but more evidence is pointing to the drug's benefits for the heart and liver. "As the guidelines by the ADA and the Liver Society are coming out, they will make doctors aware that they have a compelling reason, not a cosmetic reason, a compelling reason to prevent cirrhosis," he says.

Cusi understands there are some patients who may not be as motivated as others to lose weight, but he also has patients who have sincerely tried and find it difficult to lose weight and even more difficult to keep it off. "When you put them on these medications, they drop many, 5%, 10%, 15%, 20% of their body weight," he says. "There's clearly something beyond the stereotype that we have this kind of negative view of people who have excess weight. We have these tools: Structured weight loss programs work, increased physical activity works. Anything that gets you to get into a negative calorie balance will help your liver get healthier, and your cardiovascular disease, and your diabetes, and everything else."

And again, endocrinologists are primed to help these patients from progressing to cirrhosis and worse, starting with a simple, inexpensive test. Cusi says he hears, "There are no FDA-approved medications, so let's just wait." "In the meantime, your family member is drifting into cirrhosis, just because the doctors have not taken the time to do a simple test," he says. "Preventing cirrhosis, you also prevent liver cancer. What many doctors and patients don't know is that people with type 2 diabetes have a threefold chance of getting liver adenocarcinomas, what we call hepatocellular carcinomas. So, you are preventing cancer with a screening." EN

– BAGLEY IS THE SENIOR EDITOR OF *ENDOCRINE NEWS*. IN THE AUGUST ISSUE, HE WROTE ABOUT THE DEBUT OF ENDOCRINOLOGY MENTOR DAY AT **ENDO 2023** IN CHICAGO.



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As part of the annual Rally for Medical Research, the Endocrine Society will join with hundreds of researchers, physicians, and patients to urge Congress to support increased funding for medical research.

Endocrine Society Rallies for Medical Research as Congressional Deadline to Fund Government Approaches

The federal government is funded through an annual appropriations process in which both the House of Representatives and the Senate develop funding bills to support 12 different areas of the government, iron out differences, and pass bills by a September 30 deadline or risk shutting down the federal government.

The funding bill that covers most health programs, including the National Institutes of Health (NIH), is known as the Labor-Health and Human Services – Education and Related Agencies bill (L-HHS). It is one of the most controversial bills because it sparks partisan fights over what the federal government should spend money on, and it often includes policies that impact healthcare delivery and research. Every September in recent history, Congress has either missed or come close to missing the deadline. To protect against missing the deadline and forcing a government shutdown, Congress can pass a short-term continuing resolution that continues funding at the previous year's levels (flat funding) for a period of time. This year, the likelihood of Congress missing the deadline and even shutting down the government is particularly high because of how far apart Democrats and Republicans are in their proposals. Specifically, some conservatives in the House of Representatives are unhappy with the debt ceiling deal and demanding more cuts while Democrats are seeking funding increases in certain social programs, including the NIH.

The Endocrine Society has prioritized advocating for funding for the NIH. We have submitted testimony to the House and Senate Appropriations committees, we have met with many offices, we conducted a Hill Day earlier this year where our members met with their congressional delegations to share the value of endocrine research, and we have launched online advocacy campaigns that hundreds of our members have joined. In September, we will increase our efforts to protect the NIH from cuts and a government shutdown. Several of our members will come to Washington, D.C., to participate in a research community-wide Rally for Medical Research to urge Congress to support funding. Together with hundreds of researchers, physicians, and patients, we will continue to call on our nation's policymakers to make funding for the NIH a national priority and raise awareness about the importance of continued investment in medical research that leads to more progress, more hope, and more lives saved.

If you cannot join us in Washington for the Rally for Medical Research Hill Day, we encourage you to join our efforts by visiting **www.endocrine.org/takeaction** and participate in our online advocacy campaign. Our campaign will provide you with a template message and direct that message to the correct mailboxes of your senators and representative. If you have received NIH funding for your research, it is critical that you let your elected officials know how important this is. This will take less than a minute of your time but will make a difference to the outcome.

European Parliament Dances Around EDC Legislation

The Endocrine Society has worked in the European Union (EU) to advance legislation to regulate endocrine-disrupting chemicals (EDCs) consistent with the ambitions of the EU Green Deal. As the European Parliament returns in September following the summer recess, legislation is moving forward in certain areas, but a comprehensive approach remains just beyond the horizon for the time being.

We are pleased to see progress on several important legislative initiatives. In July, the European Commission published a proposal to update laws on toy safety with specific bans on EDCs. Consistent with the Society's recommendations, the proposal covers both known and suspected EDCs with strict limits on exemptions and an obligation for agencies to consider combination exposures. In addition to this "sectoral" approach to legislation, the Commission also has signaled plans to follow up on the decision by the European Food Safety Agency (EFSA) to dramatically lower the tolerable daily intake level of bisphenol A (BPA) by working on amendments to the Food Contact Materials Legislation that would impose strict controls on BPA in foodstuffs.

While these are important developments and the Society celebrates these milestones in public health protection, more ambitious measures are required to minimize exposures for all populations. As of mid-August, the Commission had yet to deliver proposals for updating the regulation on Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) with measures to restrict EDCs based on the categories currently recognized in other legislation passed last year. We are also concerned that the legislative proposals targeting BPA would not cover so-called regrettable substitutions such as BPF and BPS, which may have similar effects on endocrine health.

The forthcoming REACH initiative is critical as it will provide a more comprehensive approach to restrictions on harmful chemicals, and the public health community has recognized the need to update this critical legislation to reflect the latest science on EDCs and other hazards. The Commission has repeatedly stated that it intends to publish proposals on REACH by the end of 2023, and the Endocrine Society's EU EDC Task Force is ready to assess these proposals and develop our position once published, but even if the text of a legislative proposal is delivered as promised, the likelihood of the legislation progressing into law within the current term is extremely small. Recognizing this, the Society will work with our members to make as much progress on our goals in the current term and set the stage for results following the EU elections.

> **"Our Task Force members will connect with our champions in the European Parliament to ensure that the final regulations are sufficiently strong and backed by science."**

We expect September to be a busy month as the Parliament will take up the legislation on toys and the Commission will collect input on potential controls for BPA. Our Task Force members will connect with our champions in the European Parliament to ensure that the final regulations are sufficiently strong and backed by science. We will also point to ongoing efforts to consider category-based approaches for regulating bisphenols in the environment, and for addressing per- and polyfluoroalkyl substances (PFAS) as a class, as appropriate paths forward for chemical classes of concern.

As fall progresses, there will be opportunities for our members in the EU to contact policymakers on these issues. If you are interested in being an advocate for better regulation of EDCs, please contact Joe Laakso, director of science policy at: **jlaakso@endocrine.org**.

Society Works to Advance Obesity Legislation in Congress

The Endocrine Society continues to be a vocal advocate to advance legislation that would address prevention and treatment of obesity.

In late July, legislation known as the Treat and Reduce Obesity Act (TROA) that the Society endorsed was introduced in the House and the Senate. This important bipartisan legislation would take steps to ensure that Medicare beneficiaries have access to the full range of obesity treatment options. Specifically, TROA would remove restrictions pertaining to Intensive Behavioral Therapy (IBT), which is an effective lifestyle intervention for obesity that includes dietary and nutrition assessment to promote weight loss. Current Medicare rules have placed restrictions in the referral process of IBT that has resulted in underutilization of the benefit.

The legislation would also ensure that Medicare beneficiaries can access Food and Drug Administration (FDA)-approved anti-obesity medications, which are scientifically proven to be effective at treating obesity. Medicare is currently prohibited from covering anti-obesity medications. The Society worked closely with the sponsors of TROA prior to the bill's introduction and shared our endorsement of the bill with other congressional offices to gain support.

The Society also continues to educate Congress about the issue of obesity. In July, the Society conducted a briefing to educate members of Congress and their staffs about the impact of obesity on children and adolescents in the U.S. We are planning another briefing in the fall to discuss the effectiveness of obesity treatment and care. We also continue to share our educational resources on obesity including the Obesity Playbook. The Playbook offers a "101" education about obesity and includes information about obesity prevalence, policy options that Congress can implement to treat obesity, existing programs from the administration and federal agencies that address this epidemic, and a list of Endocrine Society members who are obesity experts. The Playbook and other educational resources on obesity are available on the Society's website (**www.endocrine.org/advocacy/priorities-and-positions/obesity**). EN

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